TROPICAL MEDICINE

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BY

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PREFACE

Previous new editions of this book have been called for at progressively diminishing intervals of about five, four, three, and two years so that the late appearance of this issue needs a word of explanation. Strangely enough the delay was caused by the further increase in the rate of sales of the last, 5th, edition of which a reprint had to be prepared because in the conditions prevailing at the time, it was impossible to arrange for a new edition.

The subsequent release for publication of many wartime discoveries indicated that considerable changes were necessary in the light of the newer information thus made available, if the volume was to continue to fulfil its purpose. In these circumstances we have felt that a thoroughly revised and up to date edition on the lines that have proved so acceptable in the past may be found useful by readers of the classes for whom the book is intended. We have always kept specially in mind the needs of medical students and of the large body of practitioners who work in conditions in which they cannot enlist the help of modern laboratories. Special stress has, therefore, been laid on the methods of diagnosis that can be practised with the help of a microscope and a few simple appliances. We know from long personal experience of these two classes of workers how difficult is their task and we have tried to make this easier by providing them with simple guidance in the diagnosis, treatment and prevention of the common " tropical " diseases. If the student of tropical medicine can acquire a clear mental picture of the more important maladies he will have no difficulty in adding to his knowledge by consulting the excellent larger books that are available.

Although the general scope of the book remains the same as before it has not been possible to avoid some increase in its size ; room had to be found for a description of the new advances which have been made in the past few years, especially in connection with treatment. At the same time reference to older methods, even when these are much less effective, cannot be omitted because many of the new drugs are still prohibitive in price for backward communities. Difficulty in obtaining these expensive remedies is not, however, an unmixed evil ; their indiscriminate administration has already been found to produce harmful effects, such as the appearance of drug-resistant strains of organisms, interference with the development of immunity and damage to the beneficent intestinal flora. This criticism applies specially to the new antibiotics but it is not intended to discourage their use in suitable cases for which they are often the only means of saving life and preventing prolonged disablement ; it is meant as a warning against the tendency to abuse remedies which when given unnecessarily are likely to do positive harm.

In this edition there has necessarily been a great deal of revision and rewriting. We gratefully acknowledge the valuable help of Sir George McRobert who has thoroughly revised the chapters on Malaria and Dietetic Diseases and has written a note on Other Helminthic Diseases. He has also given ungrudging assistance in proof correcting and in seeing the book through the press. The appointments held by him till recent times in the tropics and now in London show how well qualified he is to write on the very important subjects in which he has collaborated.

Special acknowledgement is due to the *Tropical Diseases Bulletin* which is indispensable, not only for all writers on tropical diseases but also for every medical worker who has to deal with these diseases.

Our thanks are due to our publishers who have co-operated with their usual efficiency and courtesy.

LEONARD ROGERS
J. W. D. MEGAW

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CHAPTER I

MALARIA

(Malarial Fever, Ague, etc.)

Definition. Malaria in man is a disease caused by one or more of the human malaria parasites.

There is nearly always fever at some stage of the disease, but some cases are afebrile throughout their course. The fever is usually intermittent with quotidian, tertian or quartan periodicity; sometimes it is remittent or even continued.

The word "malaria" is derived from two Italian words, *mal* (bad) and *aria* (air): this name was applied because of the old belief that the disease was due to the inhalation of poisonous emanations from the ground, especially in marshy places. The name dates from 1753.

History. The disease in some of its easily recognisable forms was known thousands of years ago; periodical attacks of fever coming with shivering and passing off with sweating were naturally regarded as being due to a special disease. Hippocrates described quotidian, tertian and quartan fevers, but many forms of malaria could not be recognised until the discovery of the malaria parasite. The history will be dealt with in some detail because of the great importance of malaria, and because the disease is an outstanding example of the manner in which progress has been made in acquiring knowledge of tropical medicine. An interesting point is that a satisfactory method of treatment of malaria was known before the cause of the disease was discovered.

An interesting, perhaps mythical, tradition is that about 1630 the Countess Cinchon, wife of a Spanish Viceroy of Peru, was cured of malaria by the bark of a tree which grew in Peru and that the cinchona bark was introduced into Europe about 1638.

In 1820 the alkaloid quinine was isolated from cinchona bark by two French chemists, Pelletier and Caventou. Quinine soon replaced cinchona bark in the treatment of malaria.

In 1847 Meckel described the characteristic pigment which he found in the blood and tissues in fatal cases.

In 1848 Virchow noticed that the pigment occurred in cells which resembled white blood corpuscles.

In 1875 Kelsch observed pigment granules in the blood corpuscles of persons suffering from malaria.

In 1880 (November 23rd) Laveran announced the epoch-making

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cases of human malaria, used sparrows infected with bird malaria. He found that the parasite underwent a remarkable development in the stomach-wall of culex mosquitoes which had fed on infected sparrows. The first change observed was the formation of the same kind of pigmented bodies as he had seen in 1897; in a few days these became greatly enlarged and finally burst, discharging thread-like bodies (now known as sporozoites) into the body cavity of the mosquito; these bodies then penetrated the salivary glands of the mosquito.

He next demonstrated that the infection was conveyed from infected to non-infected sparrows by the bites of mosquitoes, and also that control sparrows remained free from disease if protected from mosquitoes. These observations, combined with his significant discovery of the previous year, fully justified him in announcing that human malaria was conveyed in a similar way by the bite of infected mosquitoes; he also advocated the control of malaria by anti-mosquito measures.

In 1898-99 Bignami, Grassi and Bastianelli, who had been kept informed of the discoveries of Ross, reported some months later that the same cycle of events took place in anopheles mosquitoes which had fed on human beings infected with malaria. Ross had already predicted with confidence that this would be found to be the case; he was only prevented from carrying out the final confirmatory stages of his experiment by lack of opportunity and ill-health.

In the same year Koch and Pfeiffer also confirmed the findings of Ross, using the human malaria parasite, but, unlike Grassi, they did not claim the credit for discovering the means by which the disease was transmitted.

Manson played an important part in this discovery; Ross was his pupil and was indebted to him for the incentive and opportunity to carry on his work, but the conveyance of the parasite by the bite of a mosquito was no part of Manson's hypothesis. At the same time it is clear that Ross would never have made the great discovery but for Manson, a fact which Ross himself always emphasised.

The later history of malaria consists chiefly in the working out of a great mass of details in connection with the conditions in which certain anopheles mosquitoes transmit the disease, and the practical application of the discovery of Ross to malaria control. Ross was greatly mistaken in his optimistic belief that the whole scientific world would promptly apply his discoveries to the prevention of malaria. Even to-day, despite many successful efforts to control the disease, it is true that over the greater part of the malaria-stricken areas of the world the anopheles mosquito continues its deadly work as actively as if Ross had never existed.

The imagination of the world was remarkably captured by experiments carried out in 1900, when Sambon, Low, Terzi and two servants spent the whole of a malaria season in a highly-infected place

discovery of malarial parasites in the blood; he described amœboid, crescentic and flagellating forms of the parasite.

Laveran's announcement was received at first with great scepticism, several years passed before the discovery was universally accepted.

In 1883 Marchiafava, employing for the first time dried blood films stained with methylene blue, found ring forms; he claimed that these were the true parasites and that the bodies described by Laveran were not genuine. It must be remembered that Laveran made all his earlier observations on moist blood preparations; the drawings which accompanied his original paper leave no doubt as to the genuineness of his discovery.

In 1883 King gave a number of reasons for believing that malaria was transmitted by mosquitoes. For many years there had been a popular belief in several parts of the world that mosquitoes were responsible for malaria, but King was the first to give good reasons for this view.

In 1885 Marchiafava and Celli produced the disease by inoculating human beings with infected blood.

In 1885 Golgi described the stages of growth of the quartan parasite in red blood corpuscles and showed that quartan periodicity was associated with the three-day cycle of development of the quartan parasite. Soon afterwards he showed that a two-day cycle of development occurred in the parasite of benign tertian malaria.

In 1893 Smith and Kilborne proved that piroplasmosis of cattle could be conveyed by ticks. This discovery, though not connected directly with malaria, was of great importance, being the first case in which a disease was proved to be communicable by the bite of an arthropod.

In 1894 Manson suggested that the "flagellating bodies" of malaria parasites might escape from infected mosquitoes which chanced to drown in water. He thought that infection might be conveyed by swallowing water infected by the flagellating bodies.

In 1897 MacCallum observed the fertilisation of the halteridium parasite of birds. If this observation had been known by Ross it would have greatly facilitated his research.

Up to this time nothing definite was known of the means by which malaria was conveyed. Nobody suspected that the discoveries of Smith, Kilborne and MacCallum might have a bearing on the malaria problem; yet in a sense these discoveries were the labour pains of the great birth which was about to take place.

In 1897 (August 20th) Surgeon-Major Ronald Ross, of the Indian Medical Service, found pigmented bodies (now known as oocysts) in the stomach-wall of two "dapple-winged" (now known as anopheles) mosquitoes which he had previously caused to feed on persons suffering from malaria.

In 1898 Ross, working in Calcutta, and failing to obtain suitable

There are three recognised " zones of malaria " :—

I. The Temperate Malaria Zone, from about 40° N. to the northern limit of the disease, which may reach beyond 60° N. In this zone benign tertian is the prevailing form, and the disease has a very patchy distribution, though in some places severe malaria occurs. Most of the area included in this zone is free from the disease.

In the corresponding zone of the southern hemisphere there is very little malaria.

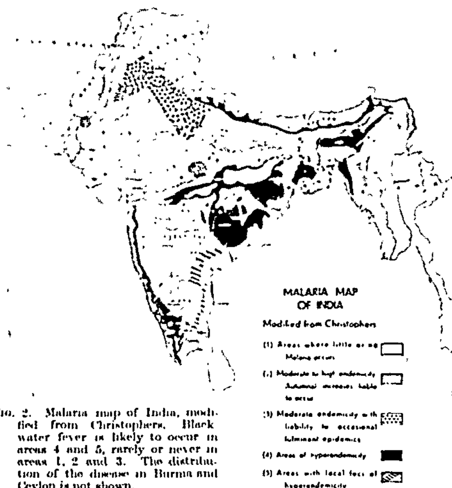


FIG. 2. Malaria map of India, modified from Christophers. Blackwater fever is likely to occur in areas 4 and 5, rarely or never in areas 1, 2 and 3. The distribution of the disease in Burma and Ceylon is not shown.

II. The Sub-tropical Malaria Zone, which lies between the tropic of Cancer and 40° N. and in the corresponding zone of the southern hemisphere.

In this zone malignant tertian malaria is common and may cause autumn epidemics ; benign tertian is also of frequent occurrence in the malarious regions of this zone.

III. The Tropical Malaria Zone. In this the malignant tertian parasite preponderates ; the disease is almost universal in its distribution and the malaria season is prolonged ; it may last throughout

in the Campagna of Italy without suffering from the disease. They lived in exactly the same conditions as the malaria-stricken people of the place, except that they remained in a mosquito-proof house from sunset till sunrise throughout the malarious season.

In the same year, anopheles mosquitoes which had fed on malaria patients in Italy were sent to London and were caused to feed on Manson, junior, and Rees, who in due course developed malaria. The conveyance of malaria by infected anopheles mosquitoes is now being carried out extensively in the treatment of dementia-paralytica, and under artificial conditions it is remarkably easy to convey the disease, even in countries where indigenous malaria does not exist.

Experimental infection of paralytics and others not naturally exposed to malaria has recently enabled Fairley, Shortt and others to establish the existence of an exo-erythrocytic stage in the life history of malaria parasites.

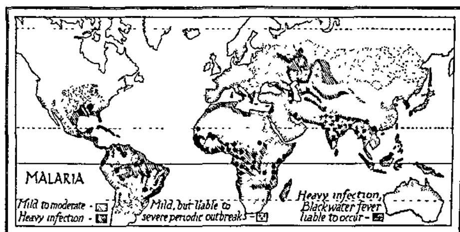


Fig. 1. Map of world distribution of malaria.

Importance of Malaria. Malaria is the most important disease of the tropics : it causes several million deaths every year, either directly or indirectly ; probably three-hundred million persons suffer yearly from varying degrees of disability due to attacks of the disease.

No accurate estimate can be made of the actual number of deaths from malaria, but it is certain that for every person who dies from an attack of the disease several others succumb to pneumonia, dysentery, etc., against which their resisting powers have been lowered by malaria. Ross suggested that some ancient civilisations, such as those of Greece and Ceylon, were destroyed by malaria. Even now large areas of fertile country cannot be properly cultivated because the inhabitants are enfeebled by malaria.

Geographical Distribution. A general idea of this can be obtained from the maps, but every doctor in the tropics ought to study the incidence of the disease in the locality in which he works. A knowledge of the local distribution of the disease is of great help in the diagnosis of doubtful cases of fever. (*See* Fig. 1 for map of world distribution.)

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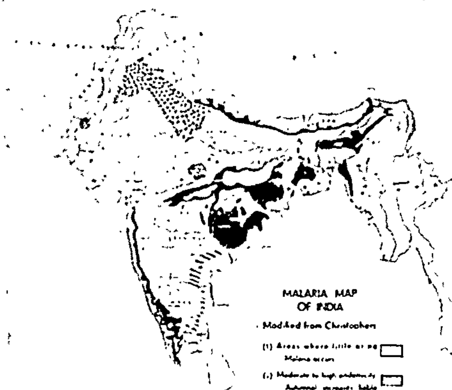


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III. The Tropical Malaria Zone. In this the malignant tertian parasite preponderates; the disease is almost universal in its distribution and the malaria season is prolonged; it may last throughout

the year in places near the equator. This zone roughly corresponds to the area which lies between the tropic of Cancer and the tropic of Capricorn.

In Australia and the Far East malaria does not occur south of 20° S. or east of Meridan 170°.

The conditions which favour the transmission of malaria are most commonly found in the tropics and sub-tropics ; in countries which have a cold winter and hot summer the disease may be prevalent if the warm season lasts long enough to allow the mosquitoes to become infected and then survive long enough to transmit the disease. Great epidemics occur only when the climatic conditions permit of the development of several successive broods of parasites in the vector mosquitoes. The parasite can also develop in mosquitoes living in heated houses even in places as far north as Archangel, and so the disease may be conveyed in the coldest weather. The distribution of malaria is often remarkably patchy ; the disease may occur in one locality and be absent from another a few hundred yards away ; in such cases the crucial factor is usually the presence or absence of suitable breeding grounds for the vector mosquitoes. The disease is often absent in the centre of large towns, even when prevalent in the outskirts and in the surrounding country.

The three chief kinds of malaria ; malignant tertian, benign tertian and quartan, differ greatly in their distribution. Malignant tertian is specially massed in the tropics ; broadly speaking, the nearer the equator the greater is its absolute and relative prevalence : it seldom extends beyond 42° N. latitude. Benign tertian is relatively more frequent in the sub-tropics and in temperate countries, where it is usually the commonest form, but it is also common in the tropics. Quartan, which is by far the least frequent type, has a very patchy distribution throughout the malarious regions of the world, although there are a few places in which it is the commonest form of malaria.

In some countries, *e.g.*, the Punjab, the disease tends to occur as great fatal epidemics in some years, while for several years in succession it may be present only to a slight extent. These great epidemics usually occur in years in which the rains are heavy and prolonged. In Ceylon, on the other hand, severe epidemics have occurred in years of exceptional drought.

In Denmark and some other countries of Europe malaria gradually died out. One plausible explanation is that the increase in the number of cattle has been the cause of the disappearance of the disease : some mosquitoes prefer to bite cattle rather than human beings, and so cease to convey the disease from man to man when cattle are available. Improved methods of agriculture, especially soil drainage, better housing conditions and improvement in the economic conditions of the people, are usually accompanied by a disappearance or diminution of

the disease, such as has taken place in England, Holland, and the Southern United States of America.

In some countries malaria has increased; for example, parts of Corsica which were formerly highly cultivated and healthy, later became very malarious, and some places in Russia became hot-beds of malaria for several years owing to the disturbances resulting from the 1914-18 War and the Revolution.

Seasonal Prevalence. As a broad general rule the chief season of prevalence is towards the end of the rainy season and in the warm season which follows the rains. In estimating the seasonal prevalence we have to consider the dates of onset of fresh attacks rather than the total number of cases observed at a given time; due allowance must also be made for the incubation period if we are to form a correct estimate of the season at which infection is most commonly transmitted. In most of the northern countries the chief season of fresh infection begins in June or July and reaches its height in August or September: with the onset of the cold season fresh infections cease to occur, yet the number of cases may not reach the maximum till October or the first half of November. The mortality often reaches its highest point in December or January; this is due to deaths from pneumonia and other diseases which attack persons who have become enfeebled by malaria. In many places there is a wave of increased prevalence of the disease in April and May, followed by a fall and a second greater wave in the autumn. In other places the disease is more common in May or June than in the autumn. Many

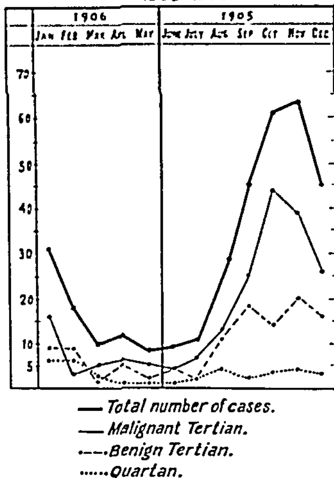


FIG. 3. Monthly admissions for malaria in Calcutta.

cases seen in spring and early summer are late relapses of attacks which occurred in the previous autumn : sometimes also the incubation period is so prolonged that persons infected in the autumn have their first attacks in the spring season. The duration of the malarious season varies greatly ; in northern countries the conditions which favour transmission exist only for a short time, and most of the fresh infections occur during a period of one to three months : farther south the season may be prolonged to four or five months, and near the equator transmission may persist throughout the year.

The number of cases of proved malaria which were brought under treatment for the first time in the Calcutta Medical College Hospital will serve as an illustration of a typical seasonal prevalence of the disease in the northern hemisphere. The chart (*see* Fig. 3) shows the numbers of fresh cases actually treated in each month, so that a correction must be made in estimating the seasonal incidence of infection. The curve of infection probably rises and falls about a month earlier than the curve of admissions for malaria.

On the whole, benign tertian infections tend to begin earlier in the year than malignant tertian. Malignant tertian gives rise to most of the explosive and fatal epidemics.

Quartan malaria is not so definitely seasonal as the other kinds of malaria.

Altitude. The disease is entirely absent at high altitudes. In Europe infection ceases at heights which vary from 1,500 to 3,000 feet according to the latitude. In India, Africa and Central America, it may occur up to about 6,000 feet. It has been reported from Quito at an altitude of 9,000 feet.

Air Temperature and Moisture. These factors have to be considered together. C. A. Gill found that the disease was not transmitted in the Punjab when the mean monthly temperature fell below 61° F., and the mean humidity below 63 per cent. The relationship of malaria transmission to temperature has not been worked out with great accuracy, but the following general statements can be made. (1) At low temperatures mosquitoes do not bite, but if a mosquito has already bitten and become infected, it can survive for long periods at low temperatures and become capable of conveying the disease in warmer weather. (2) Higher air temperature with low humidity is unfavourable to malaria, because mosquitoes survive with difficulty in these conditions. (3) The malignant tertian parasite needs rather high temperatures for its development in the mosquito and so does not spread so far north as the other two forms.

The temperature and moisture inside houses may be favourable for the transmission of malaria when conditions outside are unsuitable.

Rainfall. High rainfall is usually favourable to the spread of malaria. Gill in the Punjab for several years successfully predicted the malarial incidence in the autumn season by a study of the rainfall

for July and August There are striking exceptions to the rule that high rainfall means more malaria ; in some places heavy rains flush out the breeding grounds of the mosquitoes and so cause a diminution in the malarial incidence ; also a period of drought may cause a great increase in the pools in the beds of streams and other places, so that the vector mosquitoes multiply exceedingly. To estimate the influence of rainfall a knowledge of all the local conditions is necessary. Account should be taken not only of the total rainfall, but also of its distribution month by month

Soil Conditions. The digging of borrow-pits and interference with the natural surface drainage by building railway embankments may cause an increase in malaria Improvement in cultivation, whether from tillage, drainage, irrigation or periodical flooding, usually results in a diminution of malaria, though recent disturbance of the soil is often followed by an outburst of the disease.

Economic Conditions. When the people of a place become prosperous from improved methods of agriculture or other reasons, there is usually a fall in the incidence of malaria. Such factors as the ability to build better houses, buy mosquito-nets and quinine, eat better food and wear protective clothing, have to be considered. Other possible factors are reduction in the mosquito breeding places by tillage and drainage and increase in the number of cattle on which many kinds of mosquitoes feed in preference to human beings.

Movements of Population. When large numbers of susceptible persons move into a malarious locality the conditions become favourable to the occurrence of a severe outbreak. A striking example of this was the original attempt to construct the Panama Canal, when malaria played an important part in frustrating the work.

Organised measures for the control of malaria are now recognised as being essential to the success of any large engineering undertaking in malarious localities.

Great movements of population during and after the war of 1914–18 were often followed by intense outbreaks of malaria. In 1922 the inhabitants of certain areas in Russia migrated to Turkestan, about 2,000 miles from their homes ; on their return they brought malarial infection with them ; the disease caused havoc all over south-eastern Russia among people who had been weakened by famine. In 1923 there were more than 13 million cases of malaria in Russia, whereas before the war the maximum number was 3½ million : the disease again diminished steadily with a return to normal conditions.

Age. Young children suffer much more than adults, especially in hyperendemic areas in which children under two years of age are heavily infected, whereas the adults have acquired resistance to infection. Children form by far the most important reservoir of the disease.

Race. Negroes are partially immune, but no race is known to be

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Air Temperature and Moisture. These factors have to be considered together. C. A. Gill found that the disease was not transmitted in the Punjab when the mean monthly temperature fell below 61° F., and the mean humidity below 63 per cent. The relationship of malaria transmission to temperature has not been worked out with great accuracy, but the following general statements can be made. (1) At low temperatures mosquitoes do not bite, but if a mosquito has already bitten and become infected, it can survive for long periods at low temperatures and become capable of conveying the disease in warmer weather. (2) Higher air temperature with low humidity is unfavourable to malaria, because mosquitoes survive with difficulty in these conditions. (3) The malignant tertian parasite needs rather high temperatures for its development in the mosquito and so does not spread so far north as the other two forms.

The temperature and moisture inside houses may be favourable for the transmission of malaria when conditions outside are unsuitable.

Rainfall. High rainfall is usually favourable to the spread of malaria. Gill in the Punjab for several years successfully predicted the malarial incidence in the autumn season by a study of the rainfall

for July and August. There are striking exceptions to the rule that high rainfall means more malaria ; in some places heavy rains flush out the breeding grounds of the mosquitoes and so cause a diminution in the malarial incidence ; also a period of drought may cause a great increase in the pools in the beds of streams and other places, so that the vector mosquitoes multiply exceedingly. To estimate the influence of rainfall a knowledge of all the local conditions is necessary. Account should be taken not only of the total rainfall, but also of its distribution month by month.

Soil Conditions. The digging of borrow-pits and interference with the natural surface drainage by building railway embankments may cause an increase in malaria. Improvement in cultivation, whether from tillage, drainage, irrigation or periodical flooding, usually results in a diminution of malaria, though recent disturbance of the soil is often followed by an outburst of the disease.

Economic Conditions. When the people of a place become prosperous from improved methods of agriculture or other reasons, there is usually a fall in the incidence of malaria. Such factors as the ability to build better houses, buy mosquito-nets and quinine, eat better food and wear protective clothing, have to be considered. Other possible factors are reduction in the mosquito breeding places by tillage and drainage and increase in the number of cattle on which many kinds of mosquitoes feed in preference to human beings.

Movements of Population. When large numbers of susceptible persons move into a malarious locality the conditions become favourable to the occurrence of a severe outbreak. A striking example of this was the original attempt to construct the Panama Canal, when malaria played an important part in frustrating the work.

Organised measures for the control of malaria are now recognised as being essential to the success of any large engineering undertaking in malarious localities.

Great movements of population during and after the war of 1914–18 were often followed by intense outbreaks of malaria. In 1922 the inhabitants of certain areas in Russia migrated to Turkestan, about 2,000 miles from their homes ; on their return they brought malarial infection with them ; the disease caused havoc all over south-eastern Russia among people who had been weakened by famine. In 1923 there were more than 13 million cases of malaria in Russia, whereas before the war the maximum number was 3½ million : the disease again diminished steadily with a return to normal conditions.

Age. Young children suffer much more than adults, especially in hyperendemic areas in which children under two years of age are heavily infected, whereas the adults have acquired resistance to infection. Children form by far the most important reservoir of the disease.

Race. Negroes are partially immune, but no race is known to be

completely immune ; aboriginals who are sometimes regarded as having a racial immunity owe their freedom from the disease chiefly to acquired resistance ; they have become salted by repeated attacks in childhood.

Sex. Males and females are equally susceptible.

Estimation of Malarial Prevalence. A complete and accurate malaria survey is the task of an expert, but every medical man should find out the degree of prevalence of the disease in the locality in which he works.

(1) The most accurate method is to examine periodically the blood of all the people in the area. The percentage of persons who harbour parasites is known as the **Endemic Index** or **Parasitic Index** ; this varies from month to month and from year to year. This method is suitable when a detailed survey is being made, but is too tedious for the general practitioner.

When a survey of this kind is made, children are usually found to be much more heavily infected than adults, especially in places where the disease is constantly present in a severe form.

(2) Examination of the spleens was first employed by Dempster in the United Provinces of India in 1848. This is by far the easiest way of getting information about the incidence of the disease in any locality. The percentage of people with enlarged spleens constitutes the **Spleen Index.** This should be stated in terms of the children between two and ten years of age, because the spleens of persons living in hyperendemic areas tend to retract in adult life.

The spleen index gives a less accurate indication of the prevalence of malaria at any given time than the endemic index ; on the other hand it is probably a better index of the general incidence of the disease ; the ease with which it can be estimated is a great point in its favour. The general practitioner need not make an elaborate classification of the spleens according to size ; it is useful, however, to group them in a rough-and-ready way as "not palpable," "just palpable," "extending half-way between the costal margin and umbilicus," "to the umbilicus," and "beyond the umbilicus" (the figures 0, 1, 2, 3 and 4 may be used to indicate these variations). Health officers in malarious countries ought to make a spleen census twice a year, before the onset of the malaria season and just after it has begun to decline. The children of each locality ought to be examined separately ; the differences found in various localities give valuable information about places where measures of control are needed.

Examination of the spleens of children can easily be carried out in schools, or at vaccination inspections. If the data for a country were collected, it would be possible to make an accurate malaria map with very little expenditure of time or money.

Kala-azar is the only disease likely to give rise to serious error in forming an estimate of the prevalence of malaria. Allowance can

easily be made when this disease is prevalent: it rarely causes a high percentage of enlarged spleens among the children of any one age group.

Detection of Intensely Infected Areas. In some places the adults appear at first sight to be comparatively free from malaria, yet every newcomer gets a severe attack shortly after his arrival. In such areas the surviving adults have become immunized by repeated severe attacks in childhood. In places of this kind, examination of the spleens of young children will at once give evidence of the high prevalence of the disease.

Ætiology

Malaria is caused by human malarial parasites: these occur only in man and in certain anopheles mosquitoes which serve as the only known means by which the parasites are conveyed naturally from man to man.

Certain lower animals harbour malaria parasites, but these are not transmitted to man in natural conditions to any appreciable extent, although some of them can cause malaria in human beings by artificial inoculation.

Human malaria parasites are incapable of living in the blood of other animals, with the unimportant exception of some higher apes, hence it is unlikely that a reservoir of the disease exists among lower animals.

Three species of human malaria parasites are well recognised, viz.:—

(1) Benign tertian (*Plasmodium vivax*).

(2) Quartan (*Plasmodium malariæ*).

(3) Malignant tertian (*Plasmodium falciparum*). A fourth kind of malaria parasite is known to exist, *Plasmodium ovale*; this is of relatively small importance: it is almost confined to tropical Africa where it causes a disease resembling mild benign tertian malaria.

Malaria parasites have two distinct phases of existence: (*a*) the *asexual phase*, in which growth and multiplication take place entirely in man; (*b*) the *sexual phase*, the earliest stage of which occurs in human blood. The sexual parasites found in the blood do not cause fever, and probably are incapable of further development so long as they remain in the human body: their only role appears to be the propagation of the parasite. The greater part of the sexual phase is passed in certain species of anopheles mosquitoes which are capable of transmitting malaria. When a mosquito of a suitable kind sucks blood containing the sexual forms (gametocytes) these undergo further development, eventually giving rise to numerous slender bodies called sporozoites which lodge in the salivary glands of the insect; some of the sporozoites are injected into any person whom the mosquito happens to bite. The sporozoites enter the liver cells producing growing and dividing forms which eventually rupture the liver cell. Some of the young forms thus liberated enter red blood cells as asexual

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DIFFERENCES BETWEEN THE THREE KINDS OF MALARIA PARASITES (*refer to Coloured Plate*)

The descriptions refer to parasites seen in stained films.

	Benign tertian (*P. vivax*)	Quartan (*P. malariæ*)	Malignant tertian (*P. falciparum*)
Young forms of the parasites.	Blue signet rings, rather large, growing into irregular amœboid forms with vacuoles.	Blue signet rings, rather large, growing into compact, sometimes band-like forms, which are slightly amœboid and have inconspicuous vacuoles.	Small blue rings, often with two red chromatin dots. Sometimes two or more rings in a cell. The rings become small, compact amœboid forms, rarely seen in the peripheral blood. The rings may be very numerous at certain times.
Pigment	In fine granules, evenly distributed.	In coarse granules arranged round the periphery of the parasite.	In one or two solid masses.
The infected blood cell	Becomes enlarged and has Schüffner's dots.	No enlargement; Schüffner's dots absent: very fine stippling may be seen in intensely stained films.	Corpuscle not enlarged: it may be smaller than normal. It may have a few cleft-like dots, called Maurer's dots. There may be distortion and polychromatophilia.
Size of mature asexual forms.	Larger than a normal red corpuscle, irregular in outline.	Smaller than the red corpuscle.	Smaller than the red cell.
Number of segments.	Fourteen to twenty-four (usually eighteen to twenty).	Six to twelve (usually eight to ten).	Six to twenty-four (usually eight to ten. Rarely seen in the peripheral blood).
Duration of cycle of development in man.	Forty-eight hours.	Seventy-two hours.	Twenty-four to forty-eight hours.
Sexual forms	Round or ovoid, larger than a normal red blood cell.	Round or ovoid, about the same size as a normal red blood cell.	Crescent or sausage-shaped.
Lapse of time before mosquito becomes infective (exogenous cycle).	Ten to fourteen days or more; varies with the temperature.	Eighteen to twenty-one days or more.	Eight to eleven days or more.
Optimum temperature for exogenous cycle.	25° C.	22° C.	30° C.
Incubation period of resulting fever.	Fourteen to eighteen days or more.	Eighteen to twenty-one days or more.	Nine to twelve days or more.
Onset of fever	Sudden; rarely gradual.	Sudden; rarely gradual.	May be insidious or sudden.
Periodicity of fever	Tertian or quotidian.	Usually quartan.	Usually quotidian; may be tertian.
Usual duration of paroxysm of fever.	Six to eight hours.	Four to six hours.	Twelve to thirty-six hours or more.

1 to 42. **Protozoa and Spirochætes.** All drawn approximately to the same scale except Figs. 19, 30 and 42.

1. Trypanosome of sleeping sickness.
2. The parasite of kala-azar (cultural forms).
3. The parasite of kala-azar in a large mononuclear leucocyte.
4. The parasite of kala-azar in smear from spleen culture.
5. The parasite of oriental sore.
6. The spirochæte of relapsing fever.
7. The spirochæte of yaws.

8, 20 and 31. Normal red blood cells.

9 to 19. **Benign Tertian Parasites.**

9 to 16. Benign tertian parasites in various stages of development (asexual forms).

17. Female sexual parasite.
18. Male sexual parasite.
19. B.T. Parasites in blood smear.

21 to 30. **Malignant Tertian Parasites.**

21 to 27. Asexual forms.

28. Female crescent.
29. Male crescent.

32 to 42. **Quartan Parasites.**

32 to 39. Asexual forms.

40. Female sexual form.
41. Male sexual form.
42. Peripheral blood smear.

43 to 51. **Leucocytes.**

43 and 44. Polymorphonuclears.

45 and 46. Small lymphocytes.

47. Large lymphocyte.
48. Monocyte. The nucleus is typically kidney-shaped, not as shown in the plate.

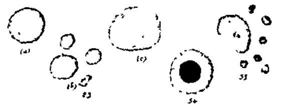
49 and 50. Eosinophils.

51. Basophil leucocyte.
52. Blood platelets.

53 to 59. **Various Red Cells, Etc.**

53. (*a*) Normal red cell. (*b*) Microcytes. (*c*) Macrocyte.
54. Normoblast.
55. Blood platelets, one imposed on red cell.


PROTOZOA ×1000


SPIROCHÆTES

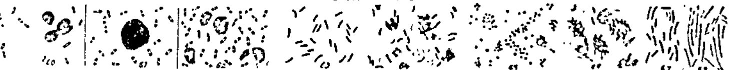

MALARIA PARASITES


WHITE BLOOD CORPUSCLES ×1000

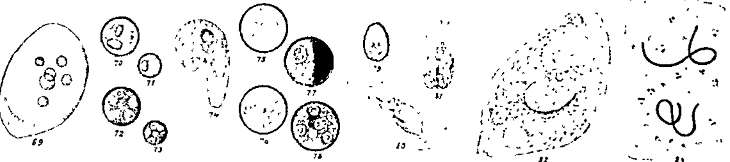

RED BLOOD CORPUSCLES AND ARTIFACTS ×1000



BACTERIA x1000



INTESTINAL PROTOZOA x500



OVA OF INTESTINAL AND OTHER PARASITES x140



56 to 58. Cabot's rings (polychromatic filament in red cell).
59. Red cell with basophil stippling.
60 to 68. **Various Bacteria.**
60. Smear of blood from rat with plague septicæmia.
61. Smear from infected gland juice.
62. Smear from sputum in plague pneumonia.
63. Cholera vibrio (culture).
64. Cholera vibrio in smear from fæces.
65. Micrococcus of undulant fever (culture).
66. Lepra bacilli in smear from nodule.
67 and 68. Dysentery bacilli (cultures).
69 to 82. **Intestinal Protozoa** (mostly after Dobell and O'Connor).
69. Vegetative *Entamœba histolytica.*
70 and 71. Unstained cysts of *E. histolytica.*
72 and 73. Iodine stained cysts of *E. histolytica.*
74. Vegetative *Entamœba coli.*
75 and 76. Unstained cysts of *E. coli.*
77 and 78. Iodine stained cysts of *E. coli.*
79. Lamblia cyst.
80. *Trichomonas hominis.*
81. *Lamblia intestinalis.*
82. *Balantidium coli.*
83. *Microfilaria nocturna.*
84 to 93. **Ova of Parasites:**
84 and 85. Ova of hook-worm.
86. Ovum of *Ascaris lumbricoides.*
87 and 88. Ova of *Oxyuris vermicularis.*
89. Ovum of *Trichurus trichiura* (or *Trichocephalus dispar*).
90. Ovum of *Tœnia saginata.*
91. Ovum of *Schistosoma hæmatobium.*
92. Ovum of *Schistosoma mansoni.*
93. Ovum of *Fasciolopsis buski.*

These illustrations are from various sources, including Neumann and Mayer's "Tierische Parasiten," Byam and Archibald's "Tropical Diseases," Dobell and O'Connor, etc.

parasites. A few days after the onset of the fever sexual parasites also begin to appear, and thus the disease cycle is completed.

For the continued existence of malarial parasites the following conditions must be complied with :—

(1) There must be human beings in whose blood there are viable sexual parasites.

(2) Suitable anopheles mosquitoes must bite these persons and then survive for several days in suitable conditions.

(3) The infected mosquitoes must bite susceptible persons.

The degree of prevalence of malaria in a locality depends on the extent to which these three conditions are complied with.

Certain species of anopheles, for example, *A. maculipennis*, convey malaria in some localities but not in others : there are several varieties of this mosquito, some of these are effective vectors while others are not.

Many different species of anopheles mosquitoes occur in various parts of the world, but in each malarious locality one or two species are chiefly concerned in conveying the disease.

The chances that any one vector anopheles will actually carry infection are small, so the disease becomes prevalent only when suitable anopheles are numerous and all the other conditions for transmission are favourable.

On the other hand Ross has shown that a few infected anopheles mosquitoes can cause a great many cases of malaria.

The following are a few examples of the many important vector anopheles mosquitoes of the world : (1) Some varieties of *Anopheles maculipennis* (Europe, Palestine and S. Africa). (2) *A. superpictus* (S. Europe and Palestine). (3) *A. sergenti* (Palestine). (4) *A. culicifacies* (India and Ceylon). (5) *A. fluviatilis* (S. India). (6) *A. minimus* (widespread in S. E. Asia). (7) *A. umbrosus* (Malaya, etc.). (8) *A. maculatus* (Malaya). (9) *A. hyrcanus* var. *sinensis* (China and Japan). (10) *A. quadrimaculatus* (Eastern N. America). (11) *A. albimanus* (Central and South America). (12) *A. darlingi* (Brazil). (13) *A. gambiæ* (Africa ; it has recently invaded Brazil). (14) *A. funestus* (Africa).

A. gambiæ, about the year 1930, was carried by steamer or aeroplane from Africa to Brazil where it spread rapidly and caused severe epidemics of malaria. The development of rapid air and sea transport has greatly increased the risk of introducing dangerous vector mosquitoes into countries which have escaped severe malaria because of the absence of effective vectors.

The Life-history of the Benign Tertian Parasite

The sequence of events in the history of the benign tertian parasite is shown in purely diagrammatical form in Fig. 4.

The human cycle of development of the parasite must be described in greater detail than is possible in the diagram.



The infected mosquito introduces large numbers of sporozoites into the body of the human host. Within half an hour they have disappeared from the blood and have invaded the parenchymatous cells of the liver. The parasite lies close to the liver cell nucleus, grows rapidly, subdivides into thousands of fragments each of which becomes surrounded by cytoplasm to form a merozoite about 1μ in diameter. The liver cell finally bursts and the escaping merozoites either (1) are destroyed by phagocytes which flock to the site of rupture or (2) invade red blood cells to produce generalised blood infection, or (3) re-enter liver cells to carry on a liver cycle. The maintenance of such cryptic liver cycles even in the absence of parasites in the circulating blood is believed to explain relapses in benign tertian and quartan infections. It is not till a few days after the bite by the mosquito that asexual parasites can first be found in the peripheral blood.

In their youngest form these are very small amœboid bodies which grow inside the corpuscle into pigmented forms with sluggish motility. After about thirty-six hours nuclear division occurs, and by the end of forty-eight hours each parasite has divided into fourteen to twenty-four nucleated segments which escape from the corpuscle by bursting through its envelope.

The parasites, when stained by Giemsa's method, are as seen in the coloured plate (Figs. 8 to 42).

Some of the segments enter other red blood cells and go through a similar development which takes about forty-eight hours to complete. During the incubation period each succeeding brood of parasites is usually much more numerous than its predecessors, so that by the end of about fourteen days there may be thousands of millions of parasites in the blood, although as a rule only a small proportion of the red blood cells contain parasites.

The first symptoms of disease usually appear about the fourteenth to the eighteenth day after infection ; exceptionally, they may appear before the tenth day ; sometimes they are delayed till one or even several months later.

For a day or two before the onset there may be prodromata ; headache, muscular pains, a feeling of uneasiness and slight fever. Each paroxysm of fever begins at the time of escape of numbers of segmented parasites from the blood corpuscles.

A Typical Paroxysm of Benign Tertian Malaria

The paroxysm of the classical type of benign tertian malaria has three stages—the *Cold*, the *Hot*, and the *Sweating*. The patient usually feels only slightly out of sorts before the onset ; then suddenly he begins to shiver, and soon is in a state of rigor with chattering teeth and pale face. He covers himself with blankets, although if the temperature is taken it will be found to have gone up already by several

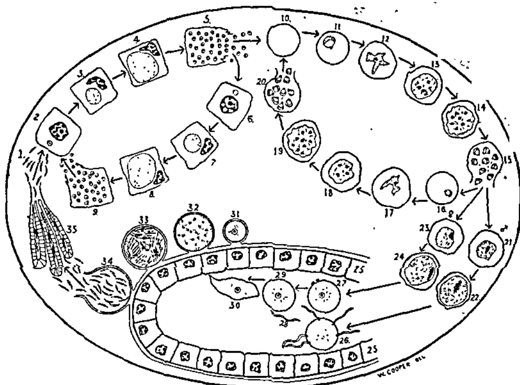


Fig. 4. *The malaria tri-cycle as seen in Plasmodium vivax infection (Shortt: Trans. R. Soc. trop. Med. Hyg.).*

EXPLANATION OF DIAGRAM

1. Sporozoites from salivary glands of mosquito enter liver cells.
2. Liver cell containing early stage of pre-erythrocytic parasite.

3 and 4. Stages in development of the pre-erythrocytic schizont in liver cells.

5. Fully developed pre-erythrocytic schizont rupturing and releasing pre-erythrocytic merozoites.
6. Liver cell containing merozoite of exo-erythrocytic cycle of schizogony.

7–9. Remaining stages in exo-erythrocytic schizogony ending in second generation of merozoites.

10. Red cell of circulating blood.

11–14. *Stages in erythrocytic schizogony in circulating blood.*

15. Fully developed erythrocytic schizont rupturing and releasing erythrocytic merozoites and gametocytes.

16–20. Repetition of erythrocytic schizogony.

21 and 22. Development of male gametocyte or microgametocyte in circulating blood.

23 and 24. Development of female gametocyte or macrogametocyte in circulating blood.

25. Wall of stomach of mosquito.
26. Exflagellating microgametocyte producing microgametes in stomach of mosquito.
27. Macrogametocyte extruding polar bodies and so becoming macrogamete.
28. Microgamete free in stomach of mosquito and seeking macrogamete.
29. Zygote, formed by fertilisation of macrogamete by a single microgamete.
30. Ookinete or travelling vermicule formed by elongation of zygote. It is about to *penetrate epithelial lining of stomach.*
31. Oöcyst, formed by oökinete after penetration of stomach wall of mosquito. It lies under elastic membrane on outer surface of stomach.

32 and 33. Stages in development of oöcyst with production of sporozoites.

34. Rupture of mature oocyst with dispersion of sporozoites most of which enter salivary glands of mosquito.
35. Salivary gland of mosquito containing mature sporozoites.

At point 5 the pre-erythrocytic merozoites (cryptomerozoites) may:—

(*a*) be engulfed and destroyed by phagocytes,
(*b*) re-enter a liver cell to continue the liver cycle as at 6,
(*c*) enter a red *blood corpuscle as at 10 to initiate* the asexual cycle.

There is no proof that re-invasion of the liver as at (2) occurs in *P. falciparum* infections.

temperature has fallen to subnormal and the patient feels comfortable, but rather exhausted.

Every day or two there is a fresh paroxysm of the same kind and unless effective treatment is carried out the attacks recur for ten days to a fortnight, when they begin to grow less severe and soon cease altogether for a few days. Each paroxysm occurs about the time when *most of the parasites are breaking up and the segments are liberated* in the blood stream : with certain modifications, referred to later, the above description applies also to the classical type of paroxysm occurring in quartan and malignant tertian malaria.

Within two or three days of the onset of the fever sexual parasites begin to appear in the blood : these play little or no part in causing fever or other symptoms; their essential function is connected with the propagation of the species of the parasite. They do not undergo further development unless the blood which contains them is swallowed by a suitable anopheles mosquito. They appear earlier in benign tertian than in malignant tertian malaria.

The so-called " typical paroxysm " is only one of the forms assumed by malarial fever : many other kinds of fever occur which are of greater importance to the medical man as they are likely to give rise to mistakes in diagnosis. The most dangerous kinds of malaria do not conform to the type just described.

Special Features of Benign Tertian Malaria

The incubation period is usually ten to twenty days, but it may be far longer, sometimes it is as much as several months.

The onset is sudden in most cases, and it is often preceded by vague premonitory symptoms. In first attacks there is usually fever of the remittent type for two or three days without the rigors and sweats that accompany the " typical " paroxysms ; then the fever becomes intermittent and is usually quotidian. In second attacks and in relapses the fever is tertian and paroxysmal in most cases from the onset, but it may also be quotidian.

The quotidian periodicity is sometimes regarded as atypical, but in reality it is so common that it ought to be regarded as one of the common forms of the disease. The explanation of its occurrence is that all the parasites do not come to maturity at the same time, often there are two distinct broods or crops at different stages of their development so that the fever becomes " double tertian " in type. In untreated cases the course of the fever is very variable ; there may be quotidian or tertian fever for anything from three days up to one or two months, the usual duration of the attack being about a fortnight or three weeks ; towards the end of the attack the paroxysms become less severe and then cease altogether, being followed by a period in which there is little or no fever. Sometimes there is no relapse, but as a rule after two to ten weeks of freedom from fever another attack

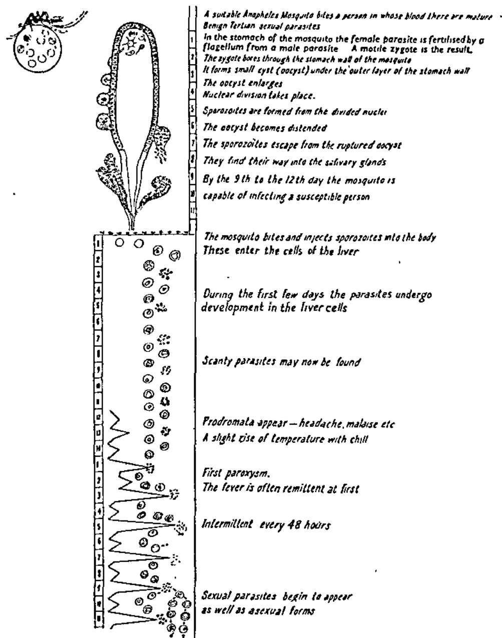


Fig. 5. Story of an attack of benign tertian malaria.

degrees. This cold stage lasts less than half an hour as a rule. Next comes the hot stage, at the beginning of which the patient is comfortable for a few minutes, but he soon begins to feel very hot ; the headache increases, the skin becomes hot and burning, the temperature rises slightly higher than in the cold stage. This stage lasts about one to six hours and is followed by the sweating stage in which the patient perspires, at first on the forehead, then all over the body : as soon as the skin becomes moist the temperature begins to fall and the patient feels greatly relieved. Within three to seven hours from the onset the

(1) The periodicity is quartan in most cases (*see* Fig. 6, Chart 1). The term "quartan fever" is somewhat confusing, the paroxysms come every three days so that each occurs on the fourth day counting the day of the previous paroxysm as the first day.

MALARIA

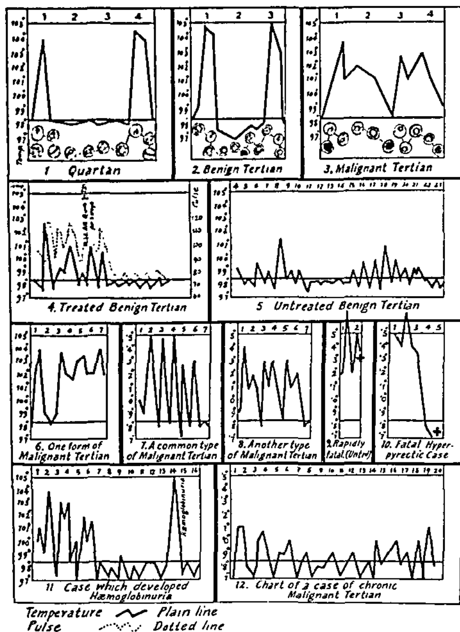


Fig. 6. Malarial temperature charts.

(2) In untreated cases the fever persists longer than in benign tertian.

(3) The paroxysms tend to be shorter than those of benign tertian.

(4) There is a persistent tendency to relapse, sometimes even for

occurs which lasts for a few days and then subsides. If the fever still remains untreated these attacks of fever, alternating with periods of freedom from fever, may go on for several months or even up to a year or more, but the attacks usually tend to become less and less severe. Very few cases are allowed to run their natural course while under observation, so that we seldom have opportunities of observing what happens in untreated benign tertian malaria. Progressive splenic enlargement and anæmia occur in untreated cases, but benign tertian malaria is seldom fatal even when no treatment is given. The importance of the disease is that it causes debility and anæmia, so that the patient becomes much more susceptible to attacks of intercurrent diseases like pneumonia or dysentery, against which he puts up a very feeble resistance. The disease tends to become chronic unless proper treatment is given. Even after the usual courses of treatment, relapses are quite common.

The chief difference between treated and untreated cases is that the former escape from the anæmia, progressive enlargement of the spleen, and weakness, which commonly result from untreated attacks.

Treatment by specific drugs, even when inadequate, is of great benefit to the patient as compared with no treatment at all.

Some special points must be noted :—

(1) There is usually a direct relationship between the number of parasites and the severity of the fever, but this is by no means constant ; cases are sometimes seen in which the parasites are very numerous, yet the fever is of moderate severity ; this feature is specially common in relapses.

(2) There may be parasites without fever.

(3) During the early days of the first attack parasites are often scanty in peripheral blood films ; they may even be absent.

(4) In children the fever is often slight and irregular ; progressive anæmia with enlargement of the spleen may be the chief, or almost the only, special features of the illness.

(5) Relapses are very common, even after proper courses of treatment ; these may occur within a few weeks, but many of them are delayed till five to eight months after the original attack ; these late relapses are often mistaken for fresh infections (*see* Fig. 9).

(6) Late relapses may be caused by exposure to cold, by fatigue, or by a surgical operation. In some such cases parasites may not be found and there may be only one or two paroxysms which cease without treatment, but a course of active medicinal treatment is desirable. Relapses have been known to occur two or even three years after the attack.

Special Features of Quartan Malaria

Quartan malaria is much less common than benign or malignant tertian ; its general course corresponds closely to that of benign tertian, but it has the following special features :—

A very important point is that the patient may have trivial symptoms for a few days and then suddenly become delirious or comatose. Every case of suspected malignant tertian malaria ought

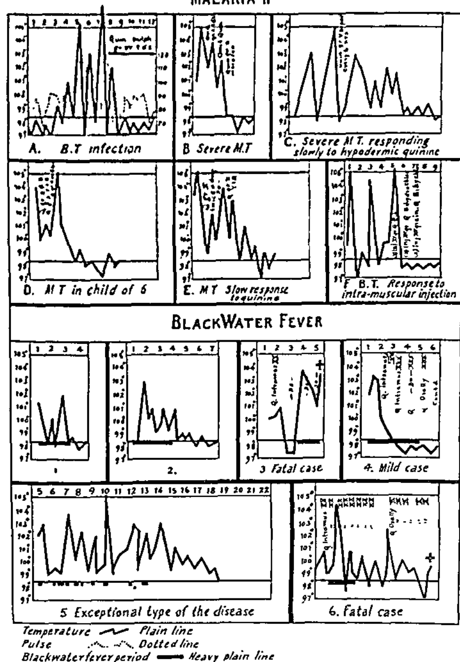


FIG. 7. Malarial and blackwater fever temperature charts.

to be regarded as an urgent emergency. The severe forms of malaria, such as cerebral or blackwater fever, are usually due to malignant tertian infection.

(6) Severe fatal epidemics are nearly always of the malignant

three or four years after the original attack. The blood has been known to remain infective for many years, as shown by cases of infection caused by transfusing blood, in one case thirteen, and in another seventeen years, after complete recovery from all clinical symptoms.

(5) *The mortality is even lower than in benign tertian,* though fatal cases are by no means unknown in heavy infections.

(6) Double quartan is the only common aberrant form; it is associated with the presence of two crops of parasites. Triple quartan may also occur, giving rise to quotidian fever, but even when paroxysms occur daily, the temperature usually rises to a higher level every three days.

(7) Diagnosis from the temperature chart is often easier than by blood examination; the parasites may be very scanty.

(8) Nephritis is common in quartan malaria; in some localities 40 per cent. of all persons suffering from quartan malaria have had subacute nephritis.

Special Features of Malignant Tertian Malaria

This is the most important kind of malaria; the following points must be emphasised :—

(1) The fever seldom conforms to the "typical" picture of malaria. The onset is insidious in many cases; the temperature chart may show step-like rise like that of typhoid fever; in such cases rigors and sweats may be completely absent. The fever may be slight, even in severe cases. There is usually intermittent fever which comes daily in characteristic paroxysms, but these are longer than in benign tertian; sometimes they overlap so that the fever is remittent or even continued. The periodicity is more often quotidian than tertian so the name malignant tertian is misleading.

The variations seen in the temperature curves are so many that no preconceived ideas should be formed as to the types of fever which *are to be expected (see Fig. 6, Charts 3, and 6 to 12, and Fig. 7, Charts* B to E).

(2) Splenic enlargement is often absent during the first few days: a patient may die without having any obvious enlargement of the spleen.

(3) Rigors are far from constant even in fatal cases.

(4) The mature forms of the asexual parasites are seldom found in the peripheral blood; quite commonly parasites cannot be found during the first two or three days of the attack unless blood smears are made every six to eight hours and thoroughly searched; even then it is by no means safe to exclude malaria because of negative findings in the first day or two of the fever. In thick films experts can usually discover the parasites on the first or second day.

(5) The general symptoms, such as delirium, vomiting, and early jaundice, demand special attention; one of these may be the only feature which arouses suspicion of malaria.

the patient has been used for human inoculation as a therapeutic measure malignant tertian infection has been caused ; fatal results have been known to follow in such cases.

In mixed infections irregular types of temperature curve are naturally more common than in simple infections.

Multiple Infections

Persons are often bitten by infected mosquitoes on more than one occasion, so that there is a multiple infection. Some of the irregularities seen in the clinical picture of malaria are due to the occurrence of *multiple infections. Probably also some of the fatalities occurring in* malignant tertian infections are due to the development of a fresh crop of parasites after the first infection has been controlled by quinine. Quinine has no action on sporozoites and very little on the parasites which first develop from these, so that a fresh infection may be developing even while the patient is being adequately treated for the original infection.

Immunity

In untreated cases each attack is brought to an end by the development of immunity ; this is usually of short duration as is shown by the occurrence of relapses. Lasting immunity is built up by slow degrees, and even when complete against the parasite which has caused the fever, it does not protect against other kinds of parasite or even against *different strains of the same species of parasite. Immunity* against malignant tertian infection is less than that resulting from benign tertian or quartan infection.

The name "*premunition*" has been given by Ed. Sergent to a special kind of immunity maintained by the persistent presence of pathogenic organisms in the body. This probably plays an important part in malaria ; there seems to be a constant discharge of toxins which stimulate the immunising mechanism of the body so that protection is given against the existing parasites as well as against others of the same kind which may be introduced later. Negroes have a partial degree of inherited immunity against malaria.

The immunity acquired by people who live in hyperendemic areas has been closely studied by Christophers in Singhbum in India.

In the indigenous population he found :—

Age periods	Percentage of spleen rate	Percentage of parasite infestation	Average number of parasites per c.mm.	Average frequency of attacks of fever
1–2	75	100	12,629	Almost continuous.
3–5	88	96	1,320	Once in twenty-five days.
6–12	72	86	1,018	Once a month.
12–16	46	50	198	Once in three months.
Adult	11	50	122	Once in six months.

tertian type; the outbreaks may appear suddenly, usually in the autumn or late summer, hence the name æstivo-autumnal.

(7) In *untreated cases* the temperature tends to fall gradually from about the end of the first week; one to four relapses may occur, each lasting about a week, and separated from one another by periods of freedom from fever of about ten days duration.

The first attack may be fatal within a few days, or any of the relapses may cause death, but *the relapses usually tend to become* progressively milder. The whole course of the disease is shorter and

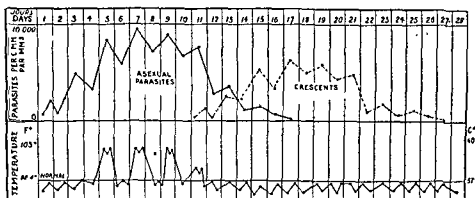


Fig. 8. Chart showing the numbers of sexual and asexual parasites at various stages of a case of malignant tertian malaria.

(From the Quarterly Health Bulletin of the League of Nations, June, 1933. After David Thomson.)

sharper than that of benign tertian or quartan, late relapses being less common.

(8) The fever requires prompt treatment with large doses of antimalarial drugs: it does not respond so readily to these drugs as the other forms of malaria, but when the fever is brought under control it does not relapse so often as benign tertian and quartan.

(9) *Certain strains of the parasite are highly virulent and need* prompt treatment with large doses of antimalarials if life is to be saved.

Mixed Infections

In highly malarious places patients often harbour two kinds of parasites; usually these are benign tertian and malignant tertian. All three kinds have been found in some cases, but there may be any of the four possible combinations of parasites: (1) B.T. and M.T.; (2) B.T. and Q.; (3) M.T. and Q.; (4) B.T., M.T. and Q. The mixed infections are more severe on the whole than unmixed infections, yet most attacks of the severest forms of malaria are caused by an unmixed malignant tertian infection.

The co-existence of *a malignant tertian infection* is sometimes overlooked in cases in which benign tertian parasites have been found; there have even been cases in which repeated examinations have failed to reveal anything but benign tertian parasites, yet when the blood of

malaria and has persisted after the other signs of the disease have disappeared.

The consistency of the enlarged spleen varies greatly; in recent cases it is soft, in old cases it may be very firm, justifying the name "ague cake."

The spleen is often so friable as to be liable to rupture by very slight injury so that in malarious countries trivial assaults are likely to have grave consequences for both of the parties concerned.

Liver. This is sometimes enlarged; tenderness in the liver region is occasionally so pronounced as to suggest liver abscess. Exploration of the liver has even been carried out in some cases in which a blood examination would have saved the patients from a dangerous procedure. Great enlargement of the liver is uncommon.

Gastro-intestinal Disturbances. Gastritis often occurs. Vomiting should arouse suspicion of malaria, especially when the material is stained with bile, though it is quite common in other fevers. Constipation is usual, but catarrh of the lower bowel with diarrhœa or dysentery is sometimes so severe as to suggest cholera, bacillary dysentery or other intestinal disease. Dysentery or diarrhœa due to other infections may, of course, co-exist with malaria.

Jaundice is common but is usually slight.

In some cases of malignant tertian infection jaundice arouses suspicion of malaria when the other symptoms are ill defined or misleading.

Circulatory System. The pulse is not characteristic; its rate usually corresponds with the height of the temperature, whereas in typhoid and dengue the pulse tends to be slower than would be expected.

The Blood. Apart from the presence of the parasites other important changes take place in the blood. Destruction of red blood cells by the parasites and their toxic products gives rise to anæmia. Even after an attack of moderate severity the hæmoglobin and red blood cells may be reduced by 25 per cent.; in severe attacks the reduction may be much greater.

The sudden fall in the number of the red cells is not entirely accounted for by the destruction of individual corpuscles by malaria parasites; hæmolysis is caused by the toxins which circulate in the blood stream. Rapidly developing anæmia is very suggestive of malaria.

Associated with the rapid and almost explosive destruction of red blood cells remarkable changes also occur in the leucocytes during the attack. Just before the onset of the paroxysm there is often a pronounced leucopenia, while at the height of the fever, and just afterwards, leucocytosis is usually observed. Apart from these temporary changes there is often a late increase in the monocytes which may become 15–20 per cent. of the total white cells in chronic cases. Leucopenia may occur in chronic malaria, but is not so pronounced as in kala-azar.

Granules of malaria pigment are sometimes seen in the monocytes

In places like this the young children suffer continuously from malaria for one to three years : *probably many of them die, but the* survivors acquire a considerable degree of immunity.

In places where malaria is less intense the immunity takes a longer time to develop and is rarely complete, even against the local strains of parasites.

Some observers hold that the treatment of malaria ought to be directed towards controlling the severe manifestations of the disease rather than the complete eradication of the infection ; there is something to be said for this view in the case of persons who are exposed to repeated reinfection because acquired immunity is of great value to them. In ordinary circumstances this immunity is acquired at too great a cost ; it involves prolonged disability and even risk to life.

THE SPECIAL SYMPTOMS OF MALARIA IN GENERAL

Fever. The common types of fever have already been dealt with.

Rigors and Shivering. Periodic attacks of shivering or rigors are usual in benign tertian and quartan malaria, but in malignant tertian they may be slight or altogether absent.

Sweating. What has been said of rigors applies equally to sweating.

Headache is usual, but is equally common in most febrile diseases, and therefore does not help in diagnosis.

Pains in the Back and Limbs. These are common and sometimes are so severe as to suggest dengue ; they are of little diagnostic significance.

Enlargement of the Spleen. In the *earlier stages* of the disease there is only slight enlargement of the spleen, and in many cases the organ is not palpable. Obvious enlargement early in the course of an attack of fever is suggestive of malaria, but by no means diagnostic ; it occurs in several other fevers.

In prolonged fevers great enlargement of the spleen is very suggestive of malaria, but it also occurs in kala-azar and various other febrile conditions.

In a large series of proved cases of malaria in Calcutta, the spleen was found to be palpably enlarged in less than 50 per cent., so that *the absence of splenic enlargement is not evidence* by which malaria can be excluded except in prolonged cases of fever. In chronic malaria the degree of enlargement is roughly proportional to the duration and severity of the disease ; in acute cases the spleen is not a reliable guide.

Cases of enlargement of the spleen with little or no fever are fairly common *in most malarious countries ;* in many of these there is no convincing evidence of actual malarial infection, and some writers describe " tropical splenomegaly " as a special condition apart from malaria, kala-azar, schistosomiasis, leukæmia and the other known causes of splenic enlargement. The balance of evidence favours the view that *in most* of these cases the enlargement has resulted from

These figures are not given as being of universal applicability, but they indicate the frequency with which patients suffering from malaria may appear to have some other disease.

In some cases appendicitis or other acute abdominal conditions have been simulated.

THE GRAVEST FORMS OF MALARIA (Pernicious Malaria)

These are merely the very severe forms of the disease, but most of them have the special feature of coming on with dramatic suddenness, often when least expected. They are usually met with in highly malarious regions and at the most malarious season of the year. It must be remembered that a patient may be living in a non-malarious place and yet have been exposed recently to severe infection while travelling or living in a highly malarious locality ; hence the necessity for making careful inquiries into the previous movements of persons suffering from fever. Unfortunate mistakes in diagnosis have often resulted from failure to observe this elementary rule.

Malignant tertian parasites are nearly always responsible for the grave forms of malaria ; usually the parasites are very numerous and the capillaries of the brain or other organs are found after death to be choked with emboli made up of red blood cells containing parasites. The usual view is that the invaded red cells become rigid and obstruct the capillary passages. Other factors must be concerned in some of the cases ; emboli are not found in hyperpyrexial and hæmoglobinuric malaria : in the latter condition the parasites may be scanty or absent even before the onset of the attack. Many cases of pernicious malaria have been reported in which no parasites could be found even after the onset.

Hyperpyrexial Malaria

This is of importance not only because of its severity but also because of its liability to be mistaken for heat stroke, especially if the previous history is not known. The condition occurs most commonly in malignant tertian malaria, and is usually associated with a heavy infection. It is also most common when high atmospheric temperature is combined with high humidity. Some of the cases are a combination of malaria and heat stroke.

Typhoid-like Malaria

The onset of malignant tertian malaria sometimes resembles that of typhoid fever. There may be a step-like rise of temperature without rigor or shivering. Even if the blood is carefully examined parasites may not be found during the first day or two ; when this happens it is sometimes wrongly concluded that the disease cannot be malaria. The symptoms may also be deceptively slight till suddenly the condition of the patient becomes critical or even hopeless. Numerous

and polymorphonuclears ; they may persist after the parasites have disappeared.

The *hæmoglobin* set free by the destruction of the red blood cells is so rapidly removed that it can seldom be detected by ordinary methods of examination. There is usually some bilirubinæmia. There is an increase in the euglobulins ; this is now regarded by some workers as the basis of the Henry reaction, which is positive in cases of malaria. The reaction in its simplest form consists in the flocculation of a suspension of melanin granules in water on the addition of a little serum from the patient. The melanin seems to act merely by making the flocculation of euglobulins more easy to detect. The reaction is also positive in kala-azar and so is of no help in the differential diagnosis of that disease.

Positive Wassermann and other luetic reactions often occur in acute malaria but when they persist up to a month after an attack they indicate syphilis or yaws. Reactions against *Brucella melitensis* in dilutions of 1 in 100 to 1 in 800 have been reported by G. Scotti as occurring in 48 out of 100 cases.

Urinary System. During the cold stage the urine is copious, pale and of low specific gravity ; when the hot stage sets in it becomes scanty and high-coloured. Urobilin can usually be detected in the urine. There is often a trace of albumen towards the end of the paroxysm. Nephritis with tube casts is common in quartan malaria in certain localities.

Respiratory System. Slight bronchitis may occur ; broncho-pneumonia is an occasional symptom.

Nervous System. Headache is usual. At the height of the fever mild delirium is sometimes observed, even in cases of moderate severity. The occurrence of mental disturbance in the early stages of an attack of fever should arouse suspicion of malaria.

In the graver forms of the disease cerebral symptoms are often prominent. Delirium, stupor, or coma, are usual features of cerebral malaria, but hemiplegia, aphasia, and epileptiform seizures, also occur in rare cases. In infants and young children convulsions are quite common. Neuritis or neuralgias of certain nerves may occur.

The Prominent Features

A. H. Proctor has given a useful analysis of the most prominent features of 429 cases of proved malaria.

The usual features of the disease, fever, etc., were seen in 363, while in 66 cases the prominent symptoms or signs did not at first sight suggest malaria ; these were made up of the following :—

Anæmia, 4 ; vomiting or gastritis, 13 ; colic, 2 ; hæmatemesis, 3 ; diarrhœa or dysentery, 11 ; choleraic symptoms, 3 ; difficulty of micturition, 3 ; bronchitis or broncho-pneumonia, 12 ; collapse, 3 ; typhoid state, 1 ; cerebral and nervous, 7 ; jaundice, 4.

Bilious Remittent Malaria

This term is falling out of use ; the disease is merely severe malaria in which there is persistent vomiting of bile-stained material.

Jaundice is a prominent feature ; the urine is bile-stained ; in most cases abdominal pain, hiccough, and vomiting occur. The condition may simulate yellow fever but blood examination will clear up the diagnosis.

Other Grave Forms of Malaria

Many diseases may be simulated : aphasia, hemiplegia, angina pectoris, syncope, asthma, broncho-pneumonia, nephritis, etc. The only way of avoiding serious mistakes in connection with these and other misleading manifestations of malaria is by making routine blood examinations in all cases of illness occurring in persons who have been living in malarious regions. Black-water fever ought to be included

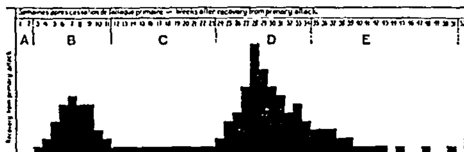


Fig. 9. Chart showing the time of occurrence of relapses in a series of cases of Benign Tertian Malaria.

(From the Quarterly Health Bulletin of the League of Nations, June, 1933.)

in the list of forms of grave malaria, but as a concession to custom it will be dealt with under a special heading.

Other Special Types

Latent Malaria. Parasites are often harboured for long periods without causing obvious symptoms ; the primary attack may occur several months after the bite by the infecting mosquito. So also relapses sometimes occur long after the apparent cure ; in benign tertian these have been seen up to three years and in quartan up to four years after infection. In malignant tertian malaria relapses are rare after one year.

When a person suffering from latent malaria is operated on, the disease may flare up and interfere with recovery. A preliminary blood examination and investigation of the history often point to the advisability of giving a course of specific treatment before operating on persons who have had malaria or have lived in malarious places. Post-operation fever should not be attributed to malaria unless parasites have been found and sepsis has been excluded.

parasites will then be found, but sometimes too late to save the patient's life.

Malaria and typhoid fever may occur at the same time, giving rise to the condition called "typho-malaria," but better named typhoid fever and malaria.

Cerebral Malaria

The occurrence of cerebral symptoms is an indication of severe and dangerous infection. There is usually a gradually developing coma, but there may be delirium, epileptiform seizures, tetanic convulsions, or symptoms suggesting meningitis. Various types of cerebral paralysis are sometimes seen. *The temperature is often deceptive, it may be* only slightly raised. Cerebral symptoms may appear within two or three days of the onset, often quite unexpectedly, while the doctor is in doubt about the diagnosis of the case. Parasites are not always numerous, sometimes none have been found a day or two before the onset of the symptoms. Blocking of the capillaries of the brain by red blood cells containing parasites is the chief cause of cerebral symptoms.

Many of the cases are fatal in spite of energetic treatment. The average case-mortality is about 40 per cent.

Hæmorrhagic Malaria

Hæmorrhages from the stomach, intestines, or lungs, purpura hæmorrhagica, etc., are sometimes seen in malignant tertian malaria. The tendency to hæmorrhage is sometimes increased by quinine, pamaquin and to a lesser degree by other anti-malarial drugs.

Severe Algid Malaria

This is also known as algid pernicious malaria. The chief features are: collapse with thready pulse, cold skin, shallow breathing, in fact, the symptoms of shock; the temperature of the surface of the body is low, *but the rectal temperature is usually raised. When symptoms of* shock are associated with frequent loose rice-water stools, the term "choleraic malaria" is used: clinically, the disease may closely simulate cholera, and it is only by blood examination that the correct diagnosis can be made. Treatment as for cholera is suitable, but anti-malarial drugs must also be given if the patient is to have a chance of survival.

Another closely related form is dysenteric malaria, in which the stools contain mucus, sometimes mixed with blood. There may be symptoms suggestive of peritonitis or appendicitis. *The possibility of* the co-existence of malaria with cholera, dysentery, and other diseases, should always be borne in mind: when two diseases occur at the same time, the recognition of only one of them forms an incomplete, and therefore wrong, diagnosis.

does not exclude the existence of latent infection in which parasites still lurk in the liver. The patient is weak and anæmic, the face has an earthy tint and is puffy, there is often swelling of the feet and legs. Hæmorrhages of various kinds are common. The temperature tends to be subnormal, but occasional slight rises are common. The spleen and liver are enlarged, often to a high degree. The urine usually contains albumin and abundant bile pigments. The anæmia may be hypochromic, orthochromic or hyperchromic ; the higher the colour index the more likely it is that malnutrition is the chief cause.

In children there is retarded development ; in adults sterility and impotence are common.

Treatment. A course of specific therapy should be given in all cases in which there is any likelihood of the persistence of malarial infection, but the doses should never be large and a careful watch must be kept for signs of intolerance. A generous diet is of great importance, all the vitamins as well as high-grade proteins must be in good supply. Full doses of liver extract by injection and iron by the mouth should be given. Marmite is often useful.

Prognosis. In severe cases there is grave danger to life, but the outlook depends largely on the effectiveness of the treatment.

Sequelæ of Malaria

Malarial cachexia is sometimes a sequel of malaria but often it is a late stage of the disease. Apart from it the most important sequela is a state of lowered resistance to other infections such as pneumonia, bronchitis, and dysentery.

There is a temptation to regard every ailment which follows malaria as a sequela of the disease, but the following can rightly be considered as consequences of imperfectly treated attacks.

Anæmia, enlarged spleen, debility, and various disorders of the nervous system, including neuralgia, neuritis, depression, irritability, and even melancholia.

The Influence of Malaria on Other Diseases

Malaria predisposes to many other diseases, including even tuberculosis against which it used to be regarded as a safeguard.

The one disease on which an attack of malaria has a good effect is syphilis of the nervous system, especially dementia paralytica, for which induced malaria is the standard treatment.

In patients who are artificially infected with benign tertian malaria and allowed to have eight to ten paroxysms of fever great improvement is usual and up to 20 or 25 per cent. of cures have been recorded.

PROGNOSIS

Malaria may be a mild and merely troublesome disease or it may be rapidly fatal. Benign tertian and quartan infections seldom kill the

Malaria in Children

Malaria might almost be described as a disease of children ; it is more frequent in infants and young children than in adults. Most of the special points connected with malaria in children have already been mentioned, but a brief summary will be useful.

In highly malarious places the infant mortality is often very high, but as a rule far too little attention is paid to infantile malaria. The chief features of the disease are progressive anæmia and enlargement of the spleen, but among the poor and ignorant these manifestations are usually missed ; even among educated people infantile malaria is often overlooked until the child is seriously ill. The response to treatment is often slow, and relatively large doses of specific drugs are needed.

The other special characters of the disease are—convulsions are common, rigors rare, the fever is less regular than in adults and may be slight, the spleen enlarges rapidly, vomiting is common, so also is diarrhœa with mucus in the stools. Enlargement of the liver is more common than in adults. Stunted growth, infantilism, mental deterioration, epilepsy, and meningism, are other manifestations which may be the most prominent features of malaria in children.

Congenital Malaria

Parasites are occasionally found in the blood of new-born infants ; these must have entered by the placental circulation.

The disease is congenital but it must not be called inherited : *it has* been acquired in utero.

Malaria in Pregnancy

Attacks of malaria often cause abortion, miscarriage or still-birth : prompt specific treatment is essential if these accidents are to be prevented.

If available, mepacrine or chloroquine should be given, but there need be no hesitation in giving quinine ; the action of quinine on the uterus is negligible compared with that of malaria. When quinine is given the total daily dose is not diminished but the drug is given in smaller doses every four hours and small doses of bromide are also given.

Malarial Cachexia

This old name is applied to the grave *condition of debility, anæmia,* and enlargement of the spleen, resulting from repeated relapses or attacks of malaria which have *not* been properly treated.

Malnutrition usually plays an important part in causing the condition, so that in many cases it is a matter of opinion whether the name nutritional anæmia or malarial cachexia is the more suitable.

Parasites *may or may not* be found in the blood ; their absence

An equally lamentable error is failure to detect parasites which are actually present in the blood film. Malignant tertian rings are very delicate objects; they are easy to miss unless properly stained and sought by a trained eye using a good microscope. It is better not to use a microscope at all, than to make erroneous reports which may cost patients' lives.

Another common mistake is to regard a single negative report as excluding malaria. Parasites are often absent from a film taken early in the course of a malignant tertian infection; if the negative report is regarded as being conclusive the patient is *watched* for a day or two till signs of pernicious malaria appear; then a film is made, parasites are found, quinine is given intravenously, but often treatment has been started too late.

When dealing with a patient who has been exposed to risk of heavy infection the only safe rule is to assume that the disease is malaria, and to act accordingly, unless there is clear evidence that the symptoms are not due to malaria. D. K. Lindsay (1943), who has had great experience of pernicious malaria insists that every unconscious patient who has recently been in a hyperendemic area ought to be given quinine intravenously even if he has met with an accident which might have resulted from an unsuspected attack of cerebral malaria. The absence of parasites in the early stages does not exclude the disease.

The rule that treatment should be withheld till parasites have been found should be acted on only in conditions in which reliable examinations of thick films can be made twice daily and in cases in which the risk of dangerous infection can be excluded. **When in doubt, start treatment at once**; make blood smears, watch the chart, and if after two or three days there is positive evidence that the disease is other than malaria, you can omit the special treatment and await events.

An attitude of watchful suspicion is one of the first essentials in connection with the diagnosis of malaria: few cases are missed by those who are on the look-out for the disease.

Useful clues are—the history of recent residence or travel in a malarious locality, the occurrence of previous attacks, the onset of the paroxysm in the forenoon or early afternoon, rigors, jaundice and mental symptoms. These are merely grounds for suspicion, they do not justify a diagnosis. Proof of the existence of malaria consists in finding malaria parasites or malaria pigment.

The occurrence of paroxysms of fever with a regular tertian or quartan periodicity is almost conclusive.

Apparent response of the fever to drugs is sometimes misleading: in short fevers like dengue and sandfly fever the temperature often falls within a day or two, but this would have happened if no drugs had been given. On the other hand a fever which fails to respond to adequate doses of effective drugs is very unlikely to be malaria.

patient directly but when inadequately treated they lower the resisting powers against other diseases and so, indirectly, cause many deaths.

Malignant tertian, on the other hand, is a great killing disease; for example, Christophers estimated that there were 10,000 deaths in 250,000 people at Amritsar during the great epidemic of 1908.

The *chief factors which determine the mortality* are : *the species* and strain of the parasite, the intensity of the infection, the susceptibility of the patient, and the treatment which is carried out.

With early diagnosis and adequate treatment the danger to life is usually slight, but malignant tertian infection, especially in the early stages, is to be regarded as an emergency comparable with appendicitis.

The chief causes of anxiety are in :—

(1) Initial attacks of malignant tertian infection, especially when the parasites are numerous.

(2) Cases *occurring in heavily infected localities.*

(3) Cases showing drowsiness, delirium, very high temperature, symptoms of shock, hæmoglobinuria, hæmorrhages or other signs of grave infection.

(4) Cases in which diagnosis has been delayed.

DIAGNOSIS

Malaria is the disease above all others in which an early and accurate diagnosis is possible, yet disastrous mistakes are being made every day. The mistakes fall under two heads :—

(1) **A diagnosis of malaria is often made when the disease does not exist.** The *usual cause of this mistake is neglect of blood examination :* judgment and " common sense " are not enough. Some medical men in the tropics get into the way of regarding every kind of fever as malaria unless there is some other obvious cause of the high temperature ; dengue and sandfly fever are thus often diagnosed and treated as malaria, quinine is given, and when the temperature falls within a few days the diagnosis is regarded as having been confirmed by the apparent response to quinine, whereas the temperature would have fallen just as soon if no drug had been given. In such cases the ease with which a cure seems to be brought about by drugs gives rise to very erroneous ideas ; the doctor who has had numerous cases of supposed malaria which have not relapsed after a brief course of treatment is disappointed and disillusioned when he encounters real malaria with its obstinate tendency to relapse. Unskilled observers who do use the microscope have often mistaken artefacts, blood platelets lying on red blood corpuscles, or even leucocytes for parasites.

(2) **Malaria is present, but is not recognised.** This is a far more serious mistake *than the diagnosis of malaria when it does not exist.*

The mistake may be made because no blood examination has been carried out and the *symptoms have not suggested malaria to the* doctor in charge.

Having found malarial parasites, the next point is to determine the species to which they belong—the chief diagnostic points being :—

Malignant Tertian. Small rings or crescent bodies or both together may be found. The crescent bodies cannot be mistaken for anything else. The small rings may be difficult to distinguish from benign tertian or quartan *young rings, but as a rule they are smaller*; sometimes two or more are found in one corpuscle; some of them may show two chromatin dots; the containing corpuscle sometimes shows the coarse clefts called Maurer's dots.

Occasionally the older forms of malignant tertian asexual parasites are found in blood smears in addition to the small rings, but the usual finding is small rings, with or without crescents.

In benign tertian or quartan the characteristic older forms of the parasites are almost always seen in addition to the younger rings.

Benign Tertian. Parasites may be found at every stage from the young-ring form to the mature and segmenting forms; only in rare cases will all the parasites be at the same stage of development. The young rings are larger than those of malignant tertian parasites, are nearly always single, and rarely have two chromatin dots; the young amœboid forms show diffuse protoplasm with an irregular outline, the pigment is fine, the containing blood cell is enlarged and shows abundant stippling (Schüffner's dots) in well-stained films. The segmenting *forms have twelve to twenty-four segments, each of which has a red* chromatin dot; the pigment in the segmenting forms is collected in a clump in the centre. The sexual forms have a single mass of chromatin, and the pigment is diffusely distributed.

Quartan. The young ring forms are very similar to those of the benign tertian parasite. The half-grown parasites have sharper outlines and may be oval or band-shaped, the pigment granules are coarse, the red blood cells which contain the parasites are not enlarged and show no Schüffner's dots, though a very fine stippling has been demonstrated by S. P. James in strongly stained specimens. The segmenting forms have eight to twelve segments. The sexual parasites are very like those of benign tertian, but are smaller in size.

Mixed Infections. These can usually be detected by the presence of parasites which are characteristic of two or three species.

Thick Film Method

The thick film method is of great value; it is much more rapid owing to the larger quantity of blood which can be searched in a given time but the recognition of parasites is not easy for the beginner, and the film cannot be stained till at least six hours after being spread.

Spread a moderate-sized drop of blood over an area of about half a square inch of the slide, allow it to dry thoroughly in the air for six hours, keeping the film protected from flies and dust. Gently flood the film with the following mixture: glacial acetic acid, 2·5 per cent.

Malaria without Fever. Parasites may be present without causing fever ; malaria should be suspected as the cause of ill-health in persons who have been exposed to the risks of infection even if the usual symptoms are absent. A blood examination is often as helpful in revealing the real nature of a disease in malarious countries as the Wassermann test is in detecting the presence of syphilis. In infants and young children the search for malaria parasites is specially important because the symptoms so often suggest the presence of a totally different disease.

BLOOD EXAMINATION

Thin or thick smears are made and dried in air. A well-made thin film is stained by Leishman's method : four drops of the stain are applied for one minute, care being taken that the stain is not allowed to dry, then eight drops of *neutral* distilled water are rapidly added to the stain and mixed with it by tilting the slide up and down. The diluted stain is left on for ten minutes, during which time the slide is gently rocked to prevent the sediment from attaching itself to the slide ; the stain is then washed off by a stream of distilled water, a few drops of which are kept on the film for about a minute. The distilled water is then poured off and the slide dried in air in an upright position.

The film is examined with an oil immersion lens using the lowest power eye-piece first and then a higher power if necessary.

Before an object is regarded as a malaria parasite it must conform to the following conditions :—

(1) It must have the appearance of one of the recognised shapes of the parasite and be contained in a red blood cell. So-called "extra-corpuscular parasites" must be ignored.

(2) The parasite should show double staining—the protoplasmic body is blue and the chromatin body or bodies red.

(3) Pigment granules may or may not be seen in the stained parasites.

(4) Crescent bodies may occupy nearly the whole of the red blood cell : their appearance is so characteristic that difficulty is not likely to arise. The other sexual parasites may not be so easy to recognise, but when they are present some of the characteristic asexual forms will also be found in nearly every case.

(5) Pigment granules in leucocytes constitute proof of the recent existence of malarial infection, but unskilled observers often make mistakes with regard to these.

A course of practical instruction is very desirable ; the untrained beginner is extremely liable to mistake blood platelets or artifacts for parasites, also to miss delicate ring parasites which are actually present. The smear must be well made and properly stained ; the leucocytes serve as controls, if they are well stained the parasites will also be well stained.

made from each of these and examined for evidence of malaria. Parasites will be found in the blood in recent cases.

Spleen smears may show numerous parasites; the full-grown forms of the malignant tertian parasite are occasionally found even when the peripheral blood *appears to be free from infection. Pigment* granules are usually found in the reticulo-endothelial cells.

In sections of the brain cortex the capillaries are often seen to be blocked with red blood cells containing small ring parasites.

If the cut surface of the brain cortex is wiped clean with a knife-edge and then pressed for a few moments against a clean slide, the smear preparation which results may show blood casts from the capillaries; these, when stained by Leishman's or Giemsa's method, show infected corpuscles very clearly.

The liver, bone marrow, intestinal mucosa, and other organs, often show capillaries which are packed with parasites. The bone marrow of the ribs often contains numerous crescents.

Only in rare cases will evidence of active malaria be found in the dead body when careful examination with negative results has previously been made of the blood during life. Evidence of recent or old malaria may be found at the autopsy of persons who have died of some other disease: death should not be attributed to malaria unless the evidence points to that disease as the chief factor in causing death.

TREATMENT

Until recent years cinchona bark and the alkaloids derived from it —quinine, quinidine, cinchonine and cinchonidine—were the only drugs efficacious in the treatment of malaria.

As clinical suppressants they were not ideal, as gametocyticides they were useless, they were unpleasant to take and their employment —especially irregularly—in hyperendemic areas was fraught with the danger of producing blackwater fever.

Although cinchona products could be produced very cheaply under peaceful administrative conditions in Java, the relatively restricted area in which quinine is produced, its strategic weakness in time of war—hot or cold—and the almost world-wide need for anti-malarial drugs has led to an intensive search for synthetic remedies. Numbers have been made but not one of them as yet satisfies all the requirements of the ideal anti-malarial drug which should: (1) act efficiently against all species and strains of human malaria parasites; (2) act as a causal prophylactic in doses taken at infrequent intervals; (3) be so devoid of toxicity as to be capable of administration by laymen; (4) kill gametocytes; (5) very rapidly bring a clinical attack under control; (6) be so cheap that it can be issued to all sufferers.

The search for a perfect drug goes on. Large numbers of synthetic anti-malarial drugs have been produced and have supplanted cinchona products in many fields. No drug yet made kills the sporozoites of

solution in distilled water, 4 parts ; crystalline tartaric acid, 2 per cent. solution, 1 part. When the colour has been completely discharged from the film drain off the fluid and fix the film with methyl alcohol for five minutes ; then wash the film very thoroughly with neutral distilled water, pour off the water and stain with Giemsa's solution (one drop of the stock solution added to 1 c.c. distilled water) for half an hour, wash well in water and dry in air.

There are many modifications of the thick-film method ; till one of these has been mastered a thin film should also be examined in every case.

Differential Diagnosis

There are few cases in which malaria cannot be differentiated from other diseases by finding parasites. Difficulty may arise on the first or second day of malignant tertian attacks and in latent malaria : in the latter case the increase in the monocytes and the response to anti-malaria drugs will often help. The frequent coexistence of malaria with other diseases is important, the mere finding of malaria parasites does not prove that malaria is the only, or even the chief, disease. When treatment with an anti-malarial drug fails a search must be made for other causes of the symptoms that still persist. Kala-azar, amœbic hepatitis, tuberculosis and various short fevers are the diseases most often mistaken for malaria.

Morbid Anatomy

Naked-eye Changes. The **spleen** in acute cases is slightly enlarged, the colour is dark red ; in very acute cases congestion is the most obvious change. In chronic cases the spleen is considerably enlarged, firm or hard in consistence, the colour is brown to black, the capsule is often thickened and may be adherent to the neighbouring organs owing to perisplenitis.

Rupture of the spleen may be found ; this may have resulted from trivial violence or even spontaneously.

The **liver** is congested in acute cases, pigmentation of varying degree is present ; the degree of enlargement is very variable. In chronic cases the same changes are found, but the consistency of the organ is firmer.

The **intestines.** In chronic cases the intestinal mucosa often shows the slate-coloured pigmentation described by L. Rogers ; in acute cases congestion and hæmorrhages are common.

The **brain.** Congestion and œdema of the meninges may be seen in acute cases. The surface of the cortex sometimes shows a slight degree of slate-coloured pigmentation, but it may look quite normal. Small hæmorrhages may be found in the cortex and medulla.

Microscopical Anatomy. The most striking changes are usually found in the blood, brain cortex, and spleen pulp. Smears should be

It accumulates in the body and stains tissues and skin yellow. Some persons are intolerant and may develop skin rashes, lichenoid eruptions and gastro-intestinal upset. Cerebral confusion and other psychotic conditions occasionally develop. They are generally, but not always, of a temporary nature and it is wise to withhold mepacrine from persons with a poor psychiatric background.

Mepacrine is available for parenteral use as mepacrine methane-sulphonate (atebrin musonate) 0·05–0·1 gm. intramuscularly.

Chloroquine (Aralen) a 4-amino-quinoline. Tablets 0·25 gm. Chloroquine diphosphate. A powerful suppressive and an efficient schizontocide. Acts as a suppressant if administered once a week but is not so free from toxicity as proguanil. Also of use in hepatic amœbiasis. Each tablet contains 0·15 gm. of the base.

Pamaquin (Plasmoquin). An 8-amino-quinoline. Tablets 0·01 gm. *Note the small dosage.* A powerful gametocyticide. In combination with quinine it has a specific synergistic action on the exo-erythrocytic (EE) bodies of benign tertian and quartan malaria. It is a causal prophylactic in near toxic doses, but even the normal doses frequently give rise to untoward symptoms such as nausea, epigastric pain of such severity as to suggest perforation, and cyanosis. Hæmoglobinuria has also been reported in a few cases. *Pamaquin should never be given simultaneously with mepacrine.*

Pentaquine, also an 8-amino-quinoline resembles pamaquin in use and dosage but is less toxic.

Recent research on chemo-prophylaxis and on suppression have so altered the outlook on malaria that in dealing with treatment, prophylactic treatment takes pride of place over treatment of clinical attacks. Blackwater fever is now a clinical curiosity and almost a thing of the past ; visitors to the tropics should never contract malignant malaria, educated inhabitants of the tropics and members of adequately supervised labour bodies should rarely suffer from malaria. It is not *yet possible to ensure freedom from relapse in benign tertian malaria* after suppressive treatment is stopped.

A causal prophylactic is one which acts on any intermediate stage of the parasite between the sporozoite and the asexual blood forms, *e.g.* proguanil in malignant tertian malaria.

A suppressive drug is one which prevents the development of clinical manifestations by means of the continued action of the drug on the asexual blood forms.

In malignant tertian malaria in which EE bodies are believed not to persist in the liver, suppressive treatment with mepacrine or chloroquine will produce a cure if persisted in for a sufficiently long time although these drugs are not causal prophylactics. In benign tertian and quartan malaria clinical relapses are very common after suppressive treatment has stopped, probably because of the persistence of the EE bodies in the liver.

human malaria but all the other stages of all the human malaria parasites can be affected by the action of synthetic drugs.

The different stages in the life cycle of malaria parasites show qualitative differences in their reaction to drugs and within each species—especially *P. falciparum*—certain strains show quantitative differences in their reactions to drugs so that in some places unusually large doses are needed.

TABLE SHOWING THE ACTION OF ANTI-MALARIALS ON *Plasmodium falciparum* (after Covell).

Drug	Exo-erythrocyte phase	Red cell stage asexual	Red cell stage gametocyte
Cinchona alkaloids	–	+	–
9-amino acridines (mepacrine).	–	+	–
4-amino quinolines (chloroquine).	–	+	–
8-amino quinolines (pamaquin, pentaquine).	+	–	+
Biguanides . (proguanil).	+	+	*

* Prevents full development in the mosquito.

The object of the physician is to select the drug or combination of drugs most suitable for the purpose required.

The majority of sufferers from malaria are extremely poor and are unable to pay for their medicine. Price and availability are major factors in determining the choice of specific drugs ; international economic situations, dollar and sterling areas, trade barriers and import restrictions and the possibility of erecting synthetic chemical factories in the tropics all play a part in therapeutics to-day. The cinchona products will probably be used for some time in Asia but elsewhere synthetic drugs seem to be well on their way to supplant the traditional remedies.

Synthetic remedies in present use include **Proguanil (Paludrine)** a biguanide. Tablets 0·1 gm. A causal prophylactic for *P. falciparum.* A powerful suppressant of all forms of malaria ; relatively non-toxic so it may be distributed and used by laymen ; does not kill gametocytes but weakens them so that the sexual cycle stops with an abortive oöcyst. *It does not act quickly in clinical malaria so its administration during an attack in a non-immune person should be preceded by a loading dose of mepacrine.* Except for occasional production of anorexia after prolonged use it has few drawbacks but the doses necessary for African conditions were underestimated in early publications. Reports are being received about the development of parasite resistance to proguanil ; new compounds now under trial will probably oust it from its present pre-eminent position.

Mepacrine (Atebrin. Quinacrine) a 9-amino-acridine. Tablets 0·1 gm. A powerful suppressant of all forms and most strains of malaria in doses of 0·1 gm. daily. It dissolves readily and is quickly absorbed.

objection raised against them in all parts of the tropics and is completely without foundation.

Treatment of the Clinical Attack

In all forms of malaria our first object must be to procure an alleviation of symptoms as rapidly as possible with the least risk to the patient, both immediate and remote. Secondly we try to prevent relapses and to render our patient non-infective to anopheline mosquitoes.

Proguanil, so excellent in prophylaxis and in maintenance therapy, has no place in the early treatment of a clinical attack.

Mepacrine, chloroquine and quinine act quickly and surely but in hyperendemic areas the use of quinine entails a risk of producing hæmolysis. Mepacrine is now widely regarded as the drug of choice for the first day. It is always readily absorbed from the gastro-intestinal tract—whereas quinine on occasion is absorbed with difficulty.

In a fully conscious patient a loading dose of 900 mg., *i.e.*, three 0·1 gm. tablets t.d.s. should be given on the first day.

For women and for men under 140 lb. in weight the loading dose may be 600 mg.

Alternatively, in non-blackwater areas 10 grains of quinine should be given in liquid form on three occasions on the first day.

On the second and subsequent days, up to ten days, 300 mg. of proguanil should be given twice daily.

This combined mepacrine-proguanil or quinine-proguanil treatment produces rapid alleviation of clinical symptoms, a high rate of radical cure and sterilisation of gametocytes in M.T. malaria with a minimal risk of injurious side effects.

For clinical relapses in premunised indigenous people a single dose of 300 mg. proguanil or 500 mg. of chloroquine will suffice to terminate an attack.

If chloroquine is being employed 2·5 gm. may suffice for the course : 6 tablets (each 0·25 gm. chloroquine diphosphate) on the first day and 2 tablets on the second and third days. With this drug a high blood concentration is quickly attained. It is excreted slowly.

Different strains of parasites vary greatly in their response to the same anti-malarial drug and the most suitable remedy (and its dosage) in any particular locality or circumstances is a matter for local study and evaluation.

When to Administer the Drugs. During an attack an anti-malarial drug should be administered as early as possible, the former practices of waiting till the temperature had fallen or until the bowels had moved being indefensible to-day. So too is drastic purgation with calomel—a simple vegetable laxative or a dose of fruit salts being as a rule beneficial but not essential.

Rest in bed throughout the febrile attack is advisable.

Fluids must be given in plenty. Glucose may be added to drinking

The use of suppressive treatment must never be considered as justifying relaxation of the enforcement of personal protection methods. They serve drastically to reduce the amount of recurring sporozoite injection received from mosquito bites.

Chemo-prophylactic Treatment

Different methods have to be adopted in accordance with the categories of persons concerned and the nature of the localities in which they live.

NON-IMMUNES, *i.e.*, visitors to the tropics, including long-term visitors such as members of business firms, services, military and naval personnel and their children.

(*a*) In hyperendemic areas, in places with a moderate degree of malarial infection all the year round and in the malaria season in places with a definite seasonal incidence of the disease.

One tablet (0·1 gm.) proguanil daily commencing twenty-four hours before entering the area and continuing for sixteen days after leaving it.

Alternatively chloroquine 0·5 gm. once a week acts as a clinical suppressant but is not so non-toxic as proguanil.

(*b*) In tropical places with a relatively low malaria incidence rigorous attention to personal prophylaxis by the use of nets, screens, repellents, etc., may prevent infection with malaria without resort to drugs, but chemoprophylaxis should be instituted for railway journeys and when travelling outside one's own residential area.

PARTIAL IMMUNES. Partial immunity exists in many organised labour groups—in canal works, tea estates, mines, etc. Workers brought into a heavily infected area from a distance may have little immunity against local strains of malaria. Chemoprophylaxis should be instituted on military lines, *i.e.*, daily proguanil or weekly chloroquine.

If the workers are locally recruited 2 tablets of proguanil once a week will act as a suppressive.

In all organised labour undertakings attempts should be made to institute preventive treatment amongst the women and children of the workers through school teachers, home visitors and infant-welfare workers. It is usually impossible to institute prophylaxis among infants and the very young. Malaria may kill many children in villages and outlying hamlets. Those who survive gradually acquire a degree of immunity. Circumstances at present usually compel us to encourage the development of immunity without allowing acute attacks to endanger life. This can only be done by ensuring the ready access of mothers to efficient drugs as soon as their babies develop fever—an Utopian idea in remote jungle villages but one to be aimed at.

It is most important for the doctor to emphasise that chemoprophylactic drugs do not interfere with sexual potency in any way. This is a standard

may be injected into the buttocks (10 ml. on each side). Mepacrine is absorbed into the blood very rapidly after intramuscular injection.

A very popular treatment in the tropics to-day is quinine by the intramuscular route. The doctor is certain that the patient is getting the dose prescribed and "injection treatment" commands a higher fee!! Ten grains (0·65 gm.) of quinine bihydrochloride are dissolved in 2 ml. of sterile water and injected deep into the muscles.

In giving injections into the gluteal region care must be taken not to inject the drug into the region of the sciatic nerve. It should always be given into the upper and outer quadrant of the buttock. Some doctors prefer to use the vastus externus muscle of the thigh. It is difficult to regard this procedure as justifiable save in exceptional circumstances. It was essential for fat women and young children with poor veins when parenteral therapy was needed in pre-synthetic days. It must always be remembered (1) that every intramuscular injection of quinine produces an area of dead necrotic muscle; (2) that such tissue forms an ideal medium for the growth of tetanus and gas gangrene germs. Even more precautions than usual should be taken to ensure the sterility of all instruments employed in the injection. It is safer to use the contents of an ampoule prepared by a reliable firm. The neck of the ampoule and the file should both be flamed. The syringe and the needle used should be subjected to prolonged boiling and the needle may be passed through a flame after having been fitted to the syringe by means of a flamed forceps with a no-touch technique. In no circumstances should the needle employed be fitted to the syringe by hand. The skin at the site of injection should be washed and then painted with iodine.

The experienced tropical worker sees many cases of necrotic gaping ulcers of the buttocks after badly-given injections of quinine, and tetanus and gas gangrene take their toll. There is a certain amount of evidence that *Clostridium tetani* can make its way from the bowel to necrotic areas of muscle after even aseptic injections. This theory has served as a defence in several cases but unless a defendant can prove that he has taken all precautions humanly possible a suit for damages may be lost.

Treatment of Coma. Conditions of acute coma in the tropics may not be due to malignant malaria but it is often advisable to give urgent anti-malarial treatment first and to perform a complete clinical examination later. Time counts. The effects of heat and of lack of salts should be borne in mind. Tests for sugar, ketones, chlorides and protein in the urine should not be omitted. In particular neck rigidity should be carefully searched for. The slightest degree of neck rigidity, the absence of, or *undue briskness* of, the knee jerks render lumbar puncture advisable.

Meningococcal infections in the tropics may be treated as malaria—with fatal results—on account of the presence of malaria parasites in

water and to tea with advantage. In hot places the addition of small amounts of common salt to the drinking water is advisable in order to preserve osmotic equilibrium.

Hot-water bottles and blankets should be applied during the rigor stage followed by tepid or cool sponging during the hot stage. Whilst the patient is sweating fans and punkahs should not play directly on the body as overcooling may result. Frequent changing of sheets and bed garments by an attendant gives great relief whilst the patient is sweating.

Antipyretic powders—APC, etc.—(not tablets) give considerable relief if headache is severe. Small doses of phenobarbitone relieve both the headache and a tendency to vomit. For vomiting there are many remedies, none very reliable. Three minims of tinct. iodi in a wineglassful of water, a soda and bismuth mixture with 2 minims of acid. hydrocyan. dil per dose, and iced champagne all have their advocates. What is essential is not to wait too long if vomiting is a symptom but to commence parenteral therapy at once. Vomiting usually ceases as soon as the drug begins to act; then the physician should continue therapy by the natural route—by mouth.

Parenteral Therapy. (*a*) In cerebral and algid forms of malaria. (*b*) If vomiting prevents retention of the drug in the stomach. The quickest result is produced by quinine intravenously. Ten grains (0·65 gm.) quinine bihydrochloride in 20 ml. sterile normal saline should be injected into a superficial vein in the arm or leg, very slowly—not more than 2 ml. per minute.

The dangers of intravenous quinine have been grossly exaggerated. It is true that many patients who receive quinine intravenously die, for the conditions for which this method is used are often desperate and well nigh hopeless. A condition resembling the Herxheimer reaction with sudden collapse, said to be due to the too rapid disintegration of parasites, may occasionally occur. Some physicians give 10 minims of 1 : 1000 adrenaline hydrochloride intramuscularly before giving quinine into the vein. It is never advisable to give adrenaline into a vein. If the concentration of quinine is too great or if the injection is given too quickly, venous thrombosis may result: in "blackwater" areas hæmolysis may ensue. Nevertheless it may safely be asserted that for rapid action in desperate circumstances quinine by the intravenous route is both justified and clearly indicated. The injection may be repeated in six hours' time.

In hyperendemic areas, however, it is becoming more usual to employ the safer injections of mepacrine or chloroquine by the intramuscular route.

Atebrin musonate (Mepacrine methane-sulphonate) 0·375 gm. is dissolved in 4 ml. of double distilled water and is injected aseptically deep into the muscles of the buttock. This may be repeated twenty-four hours later. Mepacrine dihydrochloride 0·4 gm. in 20 ml. distilled water

Turbidity on the addition of a few drops to urine indicates quinine or protein. If the solution becomes clear on heating protein is excluded. If protein is present, filter the heated urine and cool the filtrate. If turbidity persists quinine is present in the urine.

Even more serious is the frequency with which stock solutions of quinine in dispensaries are far below their stated stength. An extensive series of surprise checks of stock mixtures in Indian dispensaries carried out by Megaw revealed that the patients were getting on the average about one-third of the quinine which had been ordered by the doctors. This fraud was often detected, even in large hospitals, so it is not surprising that many cases of " quinine resistance " were reported.

Doubtless the same thing happens in other parts of the world ; it can easily be detected on the spot by the following test :—

Test for Stock Mixtures of Quinine

This test was devised by Megaw with the technical help of S. Ghosh and Hawley.

The test reagent is :—

Pure phosphotungstic acid . . .	1 oz.
Dilute sulphuric acid (B.P.) . .	5 ,,
Rectified spirit	12 ,,

A control solution of quinine is made up of the stated strength of the mixture to be examined, *e.g.*, 10 grains to the ounce.

Equal quantities of the reagent are poured into two narrow test tubes of the same calibre to a depth of about 2 inches (say 5 c.c.). To one tube is added a measured quantity of the stock solution ; this quantity should be about one-tenth that of the reagent. To the other tube exactly the same quantity of the control solution of quinine is added. The contents of the two tubes are thoroughly mixed by repeated inversion ; spilling of the contents is prevented by placing a finger on the mouth of each tube. The tubes are then stood in the vertical position. After ten minutes the heights of the precipitates will give a rough idea of the relative strengths of the two mixtures, but after half an hour the readings will be more reliable. The test is not accurately quantitative but it gives a prompt reply to the question whether the stock mixture is approximately of the stated strength.

If there are doubts about the purity of the quinine powder from which the stock mixture has been made, a freshly prepared solution of this can be tested in the same way against the control solution of quinine.

The measurement of the quinine solutions can be made by a pipette or simply by a fountain-pen filler suitably marked.

A handy test-case containing all the necessary articles is on the market, but anyone can easily make up an outfit at a nominal cost.

the blood. Intolerable bursting headache, bad enough to make the patient cry out, and not responding within two hours to anti-malaria therapy is another indication for lumbar puncture.

When the Blood Film is Negative. Despite a negative film—and even a thick drop preparation—treatment for malaria should be instituted at once if it is suspected on clinical grounds. For the first few hours after commencing mepacrine therapy parasites may be found more easily than before treatment so films and thick drop preparations should be made every hour for six hours after commencing treatment in film-negative cases. Fever which shows no sign of remission after forty-eight hours of adequate quinine, mepacrine or chloroquine therapy is not solely due to malaria.

In benign tertian and quartan malaria the persistent EE bodies in the liver do not succumb to the action of any one drug known at present but pamaquin or pentaquine given in combination with quinine have been found highly effective in reducing the number of relapses in these varieties of malaria.

Visitors to the tropics with a double M.T. and B.T. (or quartan) infection should undergo a standard M.T. eradication course, after which a combined course of quinine and pamaquin should be given for ten days.

Quinine sulphate 0·65 gm. (gr. 10) } t.d.s. for ten days.
Pamaquin 0·01 gm. }

Such a course may be repeated after any relapse.

In the case of indigenous peoples the one-day treatment recommended for M.T. malaria will generally suffice to control a B.T. or quartan relapse.

The Use of Cinchona Products

Whilst many believe that quinine is "on its way out," the use of cinchona products will probably persist in Asia at least for some time. The cheapest salt of quinine is the sulphate but the hydrochloride contains a higher proportion of quinine base. The main alkaloids extracted from cinchona bark are quinine, quinidine, cinchonine and cinchonidine. *Cinchona ledgeriana* grows well in Indonesia and gives an exceptionally high yield of quinine, but *Cinchona succirubra* grows better in other tropical countries, yielding all four alkaloids which—combined in conformity with standards laid down by the Health Committee of the League of Nations—form Totaquina, an active preparation cheaper than quinine. Cinchona products have a bitter taste ; evasion in mass treatment is common. Tests for quinine in the urine indicate the evaders.

Mayer-Tanret reaction for the detection of quinine in urine :—

Mercuric chloride 2·7 gm. in 450 ml. of water ;
Potassium iodide 10 gm. in 50 ml. of water ;
Mix and add 2·5 ml. glacial acetic acid.

In an acute attack in a non-immune 10 grains of quinine may be given t.d.s. after meals till the temperature becomes normal. Thereafter 10 grains may be given daily for eight weeks. The relapse rate in B.T. and quartan malaria is very high with quinine therapy alone: If available the 8 amino quinolines—pamaquin or pentaquine—are advocated for relapse prevention and gametocyte sterilisation. This synergic treatment may be commenced after the temperature has been reduced by quinine and should be carried on for ten days as already indicated.

Relapses of malaria in tropical indigenous immunes may be cut short by 5–10 grains of quinine given daily for two or three days only. As a public health measure pamaquin may be given with the quinine to sterilise the gametocytes.

Quinine in Pregnancy. Malarial fever is more likely to produce abortion than is quinine in therapeutic doses but pregnancy is a clear indication for a modern synthetic drug to be employed if available.

Toxic Action of Quinine. Quinine resembles every other effective antiparasitic drug in being a poison, but except in the rare cases of supersensitiveness it can be given with safety in the doses which have been recommended.

Some degree of cinchonism is almost inevitable after full doses; the symptoms are: ringing in the ears, dizziness, slight temporary deafness, and sometimes nausea. The occurrence of these symptoms need not cause alarm, on the contrary they show that the drug is being well absorbed.

Excessive cinchonism may be an indication that the dose has been too large, but if the dose is reduced a careful check must be maintained by blood examination to ensure that the parasites are being destroyed.

Permanent deafness is rare and occurs only after excessive dosage. Very large doses, especially if continued for long periods, may cause blindness from atrophy of the optic nerve.

The prolonged use of quinine in large doses must be avoided; it causes debility, and sometimes intolerance of the drug.

There are rare cases of natural intolerance of quinine; the condition is usually inherited; after a large, or sometimes even a small dose, the patient has one or more of the following symptoms: dyspnœa, urticaria, dermatitis, œdema of the skin, hæmorrhages of the gastrointestinal, urinary or respiratory tracts, or purpuric hæmorrhages.

If there is a suspicion of supersensitiveness quinine should never be given by the intramuscular or intravenous routes till the patient has been tested in the following way: a drop of 10 per cent. solution of quinine is applied to the skin after light scarification; redness or swelling indicates undue sensitiveness to quinine. Similar tests on other persons serve as controls.

Other Forms of Quinine. Euquinine is almost tasteless and so is suitable for children; the dose is double that of sulphate of quinine.

Alternatively a sample of the stock mixture can be sent for chemical analysis, but it is far more satisfactory to do the test on the spot.

The test can also be used to check the quinine content of pills, tablets and powders which are sold on the market ; many of these, when supplied by disreputable firms, contain much less quinine than is stated on the label. They can be dissolved in acid and tested against control solutions made up with the stated quantities of quinine. When there is a serious discrepancy samples should be sent for accurate chemical analysis.

Most of the alleged failures of quinine are due to one or other of the fraudulent practices referred to above.

Another matter deserving close supervision is the inadequate supply of anti-malarial drugs in many charitable dispensaries ; the limited budget allotment is often spent largely on less essential drugs.

The Action of Quinine

It has no action on sporozoites or on gametocytes. It acts most effectively on the young stages of the asexual parasites. Moderate doses are just as effective as the huge doses which used to be recommended: 5 grains (0·3 gm.) may suffice to treat a recurrence in a premunized person. Quinine is absorbed from the small intestine. The "insoluble" salts are absorbed as rapidly as the "soluble" ones provided that they are given in solution. The rate of absorption varies greatly according to the state of the gastro-intestinal mucosa, but absorption is complete within six hours.

Administration of Quinine

Quinine sulphate is cheaper than other forms of quinine. When given in solution it is as effective as any salt. When tablets must be used a more soluble salt such as the bihydrochloride is preferable. The most commonly employed solution contains 10 grains (0·65 gm.) quinine sulphate and 10 minims of dilute sulphuric acid in 1 oz. (30 ml.) of water.

Suggested Dosage, according to Age, Weight, etc.

Taking 1 *oz. of a mixture containing* 10 *grains of sulphate of* quinine as the full dose for a robust male weighing 10 stone or more, the dosage may be modified as follows :—

Robust males	1 oz.	10 grains
Robust females, males weighing under 10 stone, and robust youths of 12 to 16	6 drachms or about	7½ grains
Children of 8 to 12 years	4 to 5 ,, ,, ,,	5 to 6 ,,
Children of 4 to 8 ,,	3 to 4 ,, ,, ,,	4 to 5 ,,
Children of 2 to 4 ,,	2 to 3 ,, ,, ,,	2½ to 4 ,,
Children of 1 to 2 ,,	1 to 1½ ,, ,, ,,	1¼ to 2 ,,
Infants under 1 year	½ to ¾ ,, ,, ,,	¾ to 1 ,,

Body weight and vigour must be taken into account.

demands a high degree of organisation by experts; the special conditions in each country must be carefully studied before operations are undertaken.

The following paragraphs give a broad, general idea of the methods which have been found useful in addition to chemoprophylaxis with synthetic drugs already referred to.

Control by the Destruction of Mosquitoes

The complete extermination of all vector mosquitoes is the ideal *method of malarial control*; *the mosquitoes can be attacked either* in their larval or adult stage.

Larval Control. This can be carried out on a small scale by getting rid as far as possible of all collections of standing water in and near the house and by weekly oiling of breeding grounds which cannot be abolished. Unless one is an expert there is no need to discriminate between the various species of mosquitoes, all are nuisances and some that are not vectors of malaria carry other diseases.

When mosquito control is carried out on a large scale a preliminary survey by an expert is essential; amateur efforts sometimes do more harm than good; for example, cutting down jungle and even drainage have sometimes caused an increase in the number of vector mosquitoes.

Among the chief methods of larval control are: drainage, with special attention to seepage in the drained area; the training of streams, again with attention to seepage; alternate flooding and flushing of streams by dams fitted with sluice gates or automatic *syphons; the deliberate flooding of marshy ground so as to create* a clean lake in which few mosquitoes are likely to breed; the protection of wells and cisterns by wire gauze; the use of fish which devour larvæ; killing the larvæ by spraying the surface of the water with D.D.T. emulsion or by dusting with Paris green; and in the case of sun-loving larvæ the planting of dense shrubs along watercourses.

In all cases the operations must extend well beyond the boundaries of the area which is being dealt with; many mosquitoes can fly up to more than a mile from their breeding grounds.

Destruction of Adult Mosquitoes. Mosquitoes often rest during the day in dark recesses which the average room provides in great variety by such articles as curtains, pictures, cupboards, tables, chairs, beds, etc. Rooms should be kept as clear as possible of attractive resting places of every kind.

The introduction of the newer insecticides, particularly residual insecticides such as D.D.T. has completely changed the outlook on adult mosquito control. In order to be acted on by a residual spray the mosquito must actually alight on the sprayed surface. The lethal action is not immediate. By the use of D.D.T. and aerosol sprays it

Quinine tannate is also almost tasteless, the dose is nearly thrice that of the sulphate ; absorption is slow.

Other Cinchona Alkaloids. Quinidine sulphate and quinidine hydrochloride are quite as effective as the corresponding salts of quinine ; they cause less cinchonism and are often tolerated in cases in which the patients have been intolerant to quinine. Totaquina probably owes much of its undoubted efficacy to the quinidine which it contains.

Cinchonine has the same action as quinine when given in doses 50–100 per cent. larger than those of quinine.

Cinchonidine has little value.

Hydroquinine hydrochloride is claimed by some to be more effective and less toxic than quinine.

Treatment During Convalescence. Rapid recovery is usual after early and effective treatment but a course of iron and arsenic is desirable if anæmia is at all pronounced. These drugs are most conveniently given in the form of pills, or tablets. A mixture containing 3 grains of sulphate of iron and 3 minims of a solution of hydrochloride of arsenic may be given thrice daily after food. A generous diet and a change to a healthy climate will hasten recovery. The patient should be warned to avoid fatigue, exposure to cold, excess of alcohol and other conditions which depress vitality and predispose to relapses. He should also be told that a mere change to a non-malarious locality does not remove the risk of relapse. Efforts to light up latent infections by adrenaline or other provocative measures are not recommended. Any patient who has to undergo a surgical operation or other trying experience within a year or two after an attack should be given treatment beforehand to obviate the lighting up of a latent infection.

PREVENTION

Malaria can be eradicated by any one of the following :—

(1) The elimination of sexual parasites from every human host.

(2) The destruction of all vector mosquitoes.

(3) The complete prevention of bites by infected mosquitoes.

The problem, though apparently simple, has proved difficult in practice except in a few places in which the breeding grounds of the vectors have been easily controlled, for example, Ismailia.

The first striking success of malarial control on a large scale was in the Panama Canal Zone ; in Malaya, and some other countries effective control was established early in the present century by persistent and skilled efforts, but the prospect of world-wide eradication of the disease was remote until the discovery of the remarkable insecticidal properties of D.D.T. and benzene hexachloride (" Gammexane "). These, combined with modern chemoprophylactic drugs, especially proguanil, have already been found highly effective in many countries all over the world. Prevention on a large scale still

is possible practically to clear large areas of residential and jungle land of adult mosquitoes with consequential reduction in the larval population also. The interiors of buildings may be sprayed with a 5 per cent. water suspension or solution of D.D.T. in kerosene every two months. Spraying of the outside of buildings and of adjacent vegetation up to fifty yards from dwelling places deals with mosquitoes which fly in to bite and which leave without alighting on walls or furniture.

In planning a spraying campaign the dwellings of indigenous immunes should be dealt with before the houses of non-immune visitors. Aerosol solutions of D.D.T. and pyrethrins have been widely used for clearing rooms, vehicles, railway carriages and aeroplanes. The aerosol " bomb " is very useful for travellers. Hand-swatting is by no means to be despised and forms a useful adjunct to other methods of control.

Preventing Mosquitoes from Biting. This is the best method of protection that is available for the individual ; if practised by everybody in an effective manner it would also provide a high degree of malaria control in a community.

All that is needed in most cases is to prevent mosquitoes from biting between sunset and sunrise. The ideal plan is to make the house mosquito proof, using wire gauze of " 18 mesh " made of " 30 imperial standard wire." Unless properly fitted and used with intelligent care mosquito-proofing is of little value, but any one who can afford to build a house can also afford to make one small room mosquito-proof even if it means that only one window can be provided and fitted with wire gauze. The mosquito-proofing of sleeping-rooms in malarious countries might go far to solve the vast malaria problem ; at any rate, it would not be a risky experiment, for even if it should not be completely effective, the reduction in malaria and the added comfort would amply repay the trifling cost.

Mosquito curtains (" bars ") *are the most popular means* of protection against bites. Curtains of " 25/26 mesh," woven from " 30/0 " cotton are used in the British Army. These have about 12 meshes to the linear inch, not 25 or 26 as might be supposed from the technical trade description.

The curtain must be wide and the lower part should be made of stout calico, so that if the arms or legs come into contact with it, the mosquitoes will not be able to bite. The really difficult period is between sunset and bedtime. During these hours protection for the body is essential ; the legs can be protected by thick stockings or mosquito-boots which come well up the thigh, the arms and neck can easily be covered, leaving only the hands and face exposed ; these can be protected by one of the repellents, such as oil of citronella. In the army citronella preparations have been supplanted by a powerful multi purpose insect repellent with dimethyl phthalate as its chief

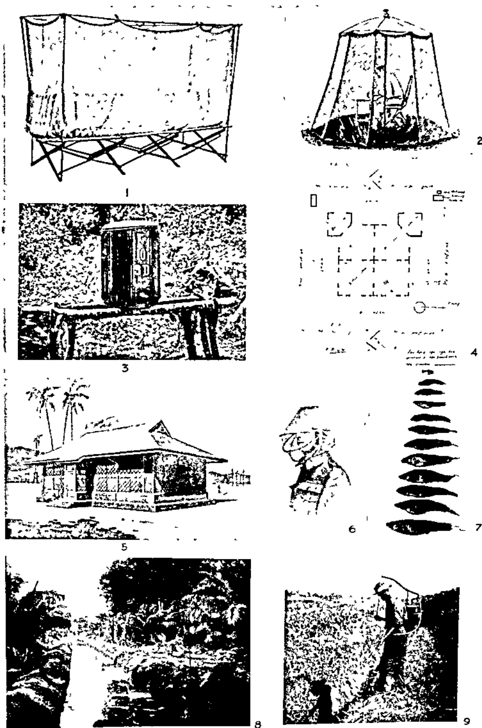


FIG. 10. Malarial prophylaxis.

1. Mosquito curtain with calico strips hung inside frame. 2. Mosquito-proof umbrella tent, Edgington pattern. 3. Vessel containing crude mineral oil dripping continuously into mosquito breeding ravine in Panama Canal Zone. 4. Plan of mosquito-proof house (James). 5. Mosquito-proof house for tropics (T. F. G. Meyer). 6. Non-inflammable mosquinette hood with perforation to permit drinking and smoking. 7. "Millions" mosquito-eating minnows. 8. Earth drain with concrete invert. 9 Meyer's knapsack oil sprayer.

conditions the haphazard selection of camping grounds may lead to disaster.

BLACK-WATER FEVER

Definition. Black-water fever is the name given to hæmoglobinuria associated with malaria infection.

Strictly speaking it is not a special disease, but is one of the many manifestations of malaria.

History. The disease has been recognised for many years in places notorious for its prevalence, but it has often been overlooked owing to confusion with "bilious remittent malaria" in which also the urine is highly coloured.

Geographical Distribution. The distribution agrees closely with

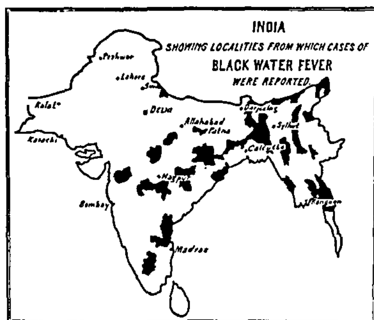


Fig. 11.

that of severe malignant tertian malaria which is transmitted during a considerable period of each year. Few cases occur in places where malarial infections are infrequent or in places subject to epidemics at intervals of several years.

It cannot originate in non-malarious localities. Many more cases occur during, or shortly after, the season of greatest prevalence of malaria than at other times. The disease is rare north of 40° N. and south of 20° S. latitude (*see* Figs. 1 and 11).

Ætiology. A good deal of mystery still surrounds the exact nature of the hæmolytic process by which the red blood corpuscles are broken down. In every attack of malaria there is a certain amount of hæmolysis but this is seldom so intense as to give rise to hæmoglobinuria.

But although malarial infection is always present, either in obvious

ingredient : Indalone, 20 parts ; Rutger's, 612, 20 parts ; dimethyl phthalate, 60 parts. Apply to exposed parts every six hours. Keep out of the eyes.

Selection of the building site is important : if the house is close to a breeding ground or to quarters occupied by infected persons, the danger of infection is greatly increased. A two-storied house is better than a bungalow ; the upper story, if airy, is less likely to be infested than the ground floor.

Some authorities hold that the keeping of cattle in the immediate neighbourhood of the house is a protection ; certain anopheles mosquitoes prefer to bite the cattle rather than human beings, especially when the cattle are kept in houses where the mosquitoes find comfortable resting places.

The Most Useful Simple Methods of Prevention

The use of mosquito curtains, especially by children, or the provision of mosquito-proofing to sleeping rooms, the use of sprays containing D.D.T., the systematic administration of chemoprophylactic drugs and such anti-larval control as is practicable are among the best of the simple methods of prevention which are of general applicability.

A valuable measure is the education of the public, especially school children and students, by simple and vivid illustrated lessons, posters, lantern lectures, cinema films, models, etc., but example is better than precept, and a well-conducted demonstration of the protection of a group of people from malaria will create a deeper and more lasting impression than any other kind of propaganda.

Special Cases. When there is reason to anticipate a heavy malarial incidence, special measures are needed ; of these the most universally applicable is to lay in a large supply of specific drugs and arrange for their distribution.

When labour forces congregate in a malarious country serious trouble must be expected unless steps are taken to institute the most careful control. An expert ought to be employed to make a preliminary survey of the region and devise measures for protecting the staff, both superior and menial. The expert must have the whole-hearted collaboration of the executive staff, otherwise he will be unable to carry out the necessary control operations.

The employment of a malarial engineer is a valuable means of securing effective co-operation between the expert entomologist and the engineering staff, as well as of devising and carrying out the necessary anti-malarial works.

Before forming a settlement in an unsurveyed country the site should be carefully selected by experts from the special point of view of malaria. Costly houses and barracks have often had to be abandoned because of the omission of this elementary precaution. In war

in practice a history of residence in an endemic area is strong presumptive evidence that an attack of hæmoglobinuria is one of black-water fever. When malaria can be excluded the diagnosis of black-water fever can also be excluded ; in such a case some other cause of the hæmoglobinuria must be sought.

(3) The disease is very uncommon in primary attacks of malaria ; it is uncommon in persons who have lived less than three or four months in the endemic locality.

(4) A few cases have been recorded in persons who have not taken any drug before the onset, but in the vast majority of cases quinine, pamaquin, or other parasiticidal drug has been taken just before the attack. In some cases a small dose is enough to precipitate an attack, in others a small dose has been well tolerated and then a larger dose has caused hæmoglobinuria. There are grounds for suspecting that pamaquin is even more likely than quinine to precipitate hæmoglobinuria, but mepacrine has been responsible for very few cases and therefore is the drug of choice when there is special risk of hæmolysis.

(5) Most of the patients who have recovered from black-water fever and who have also been completely freed from malarial infection can again tolerate full doses of quinine. This suggests that a specific hæmolytic substance is set free when the parasites are destroyed by a parasiticidal drug or that the sensitisation of the red cells ceases with the disappearance of the parasites.

(6) Even in endemic localities there is little risk of the disease if every attack of malaria is thoroughly treated. The persons most often attacked are those who are in the habit of taking quinine in a haphazard way and only long enough to check attacks of malaria. Those who take quinine regularly as a clinical prophylactic are rarely attacked.

(7) Those who have lived from birth in places where malaria is hyperendemic are rarely attacked, whereas immigrants to these places are highly susceptible to the disease ; for example, Europeans and Bengalis who go to Assam, and Egyptians who go to the Sudan. This is not a matter of inherited immunity because the young children of natives of the hyperendemic areas are liable to attacks when they are given quinine.

(8) The disease always disappears from places in which effective measures of malaria control are carried out.

(9) Exposure to cold, extreme heat, and fatigue, may precipitate an attack, even apart from the administration of quinine.

Alcohol predisposes to the disease.

The *pathological process* is as follows :—

Large numbers of red blood corpuscles are rapidly hæmolysed : the hæmoglobin that is set free in the blood is disposed of in three ways : (1) part is taken up by the reticulo-endothelial cells and converted into bilirubin and hæmosiderin ; (2) part is changed in the plasma into

or latent form, and therefore is the essential cause, malaria by itself rarely gives rise to hæmoglobinuria. In black-water fever the liberation of hæmoglobin in the hæmolytic process is greater and more sudden than that which ordinarily occurs even in severe attacks of malaria when the disease is allowed to run its natural course. There must, therefore, be another factor which is responsible for causing the rapid hæmolysis. This is usually quinine, pamaquin, or some other drug.

Quinine by itself causes hæmolysis when given in very large doses such as 60–90 grains to healthy persons ; even in therapeutic doses it has been shown by Greig to cause a moderate degree of hæmolysis in persons who have malarial infection. At the same time it must be clearly understood that quinine in ordinary doses does not cause enough hæmolysis, either in health or in the treatment of malaria, to give rise to hæmoglobinuria except in the rare cases of individual susceptibility to the drug or in the special conditions in which black-water fever occurs.

These special conditions can be stated in general terms, but the mechanism by which black-water fever is produced is not clearly understood in spite of the highly skilled research that has been directed towards its discovery.

There must be an increase in the amount of the hæmolysin or in the sensitiveness of the red blood cells to the hæmolysin or in both of these factors.

Although the hæmolysin has not been satisfactorily isolated and special fragility of the red blood cells has not been clearly demonstrated, it is likely that in certain conditions the red blood cells become sensitised by a substance resulting from the death or destruction of malaria parasites in the same way as the body cells are sensitised by the injection of foreign proteins. When this state of sensitiveness exists the further liberation of hæmolysin by the destruction of parasites causes excessive hæmolysis.

Till further light can be thrown on the process all that can be done is to consider the evidence regarding the conditions in which black-water fever occurs. This evidence is very important because of the light that it throws on the prevention of the disease.

Some of the chief points are :—

(1) The distribution of the disease, already mentioned, yields convincing evidence that it is associated with infection with malignant tertian malaria.

(2) In the cases in which blood examinations have been made just before the onset *Plasmodium falciparum* has been found in the great majority ; the actual figures reported range from 75–90 per cent. The parasites usually disappear shortly after the onset, but in most cases they reappear a few days after the end of the attack.

The preceding malaria may have been slight or even latent so that

difficulty in distinguishing the attack from one of malaria. The diagnosis of black-water fever is not justified unless there is some degree of hæmoglobinuria, but a tendency to the disease should be suspected when there is pronounced albuminuria and jaundice in a patient who has been a resident of a black-water fever locality.

Mild Type. The fever and hæmoglobinuria last for one or two days but albuminuria continues for a day or two longer.

The general condition of the patient is not seriously affected.

Moderately Severe Type. There is fever for three or four days with pronounced jaundice and hæmoglobinuria. The symptoms are those described under the heading "Special Symptoms."

Severest Type. In this the symptoms are usually severe from the onset, but sometimes the attack is relatively mild at first and there are repeated paroxysms with rapid deterioration in the condition of the patient. Suppression of urine, extreme anæmia, collapse, heart failure, hyperpyrexia, or combinations of two or more of these symptoms are the chief features of cases of this type.

Special Symptoms

Premonitory Symptoms. These are the same as in malaria, though some doctors and even patients who have had previous attacks, profess to be able to predict that an attack is imminent.

Fever. Some types are shown in the charts ; the fever is usually remittent, but may be intermittent. There may be hyperpyrexia (*see* Fig. 7, Charts 1 to 6, p. 21).

Rigors are almost invariable at the onset.

Gastro-intestinal. Vomiting is usual, epigastric pain or discomfort often occurs, there may be pronounced lumbar pain.

Jaundice. This may be moderate or intense ; it appears early and persists for a few days after the fall of the temperature.

Anæmia. This is of the same type as in malaria, but is more severe and may come on so rapidly that two or three million red blood corpuscles per c.mm. are destroyed within twenty-four hours. When the attack is over there is usually a rapid regeneration of the red blood cells.

Other Blood Changes. Parasites are seldom found after the onset, corpuscles which contain parasites being among the first to be broken down. In many cases the parasites appear again a few days after the end of the attack ; they are nearly always of the malignant tertian type. Hæmoglobinæmia always occurs but is usually slight because the hæmoglobin is rapidly excreted or taken up by the reticulo-endothelial cells so that little remains in the blood stream.

Urine. The colour is pink or bright red at first, soon it becomes dark red, brown or black, owing to the presence of blood pigments and urobilin. There is abundant albumin, more than can be accounted for by the destruction of the blood corpuscles ; albuminuria persists

a substance formerly regarded as methæmoglobin, but shown by Hamilton Fairley to be a different substance which he now calls methæmalbumin ; (3) the surplus which cannot be disposed of in the above ways is excreted in the urine which then contains albumin, oxyhæmoglobin and urobilin ; usually also methæmoglobin.

Other substances resulting from the breaking down of the red blood corpuscles and malaria parasites are liberated into the plasma at the same time ; these include granular *débris* and toxins.

The rapid excretion of these substances by the kidneys causes damage to the cells of the renal tubules ; in some fatal cases the lumen of the tubules is full of granular *débris* and there is suppression of urine.

In less severe cases the urine contains large quantities of albumin, granular *débris* and tube casts.

The hæmolysis develops rapidly and may be almost explosive in character ; the red blood corpuscles may be diminished by two to three million per c.mm. within twenty-four hours. Sometimes there is a succession of outbursts of hæmolysis at intervals for several days ; these cases are usually very severe. Advances made in our knowledge of the circulatory paths in the kidney by studies of surgical shock, the crush syndrome and severe hæmorrhage, show that in such conditions the blood may by-pass the cortical areas of the kidney, cutting off the normal flow to the glomeruli and the peripheral parts of the tubules with resulting oliguria or anuria from deficient filtration. The combined effect of this blood shunt with a paucity of efficient circulating erythrocytes results in severe renal anoxia which is now believed to account for the characteristic findings in the urinary system.

The changes found after death are those of severe hæmolysis and malaria ; the skin is jaundiced, the spleen is enlarged, soft and pigmented ; the liver is heavily bile stained, its cells are loaded with yellow particles of hæmosiderin which give the iron reaction with hydrochloric acid and ferrocyanide of potassium. Evidence of malaria is usually found in the form of malaria pigment in spleen sections ; occasionally parasites are also found. The kidneys are swollen and congested, the tubules are usually filled with *débris* and degenerated epithelial cells.

Clinical Types

The disease varies greatly in severity, some of the mildest cases are likely to be missed. In all types the onset is sudden with rigor and rapid rise of temperature ; the fever is usually remittent in type and may last for only a few hours or up to six or more days.

Jaundice and hæmoglobinuria make their appearance early in the attack.

The following types are seen :—

The Mildest Type. In this there is slight fever lasting a few hours, the hæmoglobinuria is not pronounced ; sometimes there may be

parasites are so rapidly destroyed in the early stages of the hæmolytic process that the sole reason for giving these drugs no longer exists and their only action will be to add to the toxins already in the patient's system. Quinine and pamaquin are specially objectionable because of their hæmolytic action, and even mepacrine has been known to precipitate attacks of hæmoglobinuria. In the very rare cases in which appreciable numbers of parasites persist for two days or more the question of giving mepacrine may arise, but even then the drug should be given with great caution and after anxious deliberation.

Physicians with great practical experience of the disease have found that the mortality rate has fallen sharply as soon as they ceased to give quinine as an early treatment.

No drug is known to have any action in controlling hæmolysis in black-water fever so that the treatment must be directed towards enabling the patient to overcome the effects of the destruction of his red blood corpuscles. Complete rest in bed and careful nursing are essential. A long and exhausting journey for the sake of highly skilled treatment should never be permitted ; the less the patient is disturbed the better and usually it is possible to make suitable arrangements for treatment at his own home.

Equally important is the promotion of the washing out of the toxins by supplying plenty of liquid and keeping the urine alkaline.

Treatment directed to this end must be started at once ; if the urine is acid an intravenous injection of a pint of water containing 150 grains of bicarbonate of soda should be given, and repeated if necessary. The technique described in the chapter on cholera should be adopted.

If liquids can be retained an alkaline drink such as 30 grains bicarbonate of soda to the pint of water should be given ; not less than 5 pints should be given daily. Orange or lemon juice can be added. When the urine has become alkaline as shown by litmus paper the quantity of alkali should be reduced, but the urine must be kept distinctly alkaline. If vomiting persists rectal salines to each pint of which 120 grains bicarbonate of soda are added should be given by the drip method. Salines subcutaneously or intravenous injections of 5 per cent. glucose may be needed as helps in maintaining an abundant flow of urine. Excessive administration of alkalies must be avoided ; symptoms of this are headache, giddiness, and muscular cramp. Till the acute stage is over the patient should not be given food unless he is hungry, even then weak tea with a little milk or glucose solution is all that should be allowed. The juice of two or three oranges is given daily.

Some physicians advise blood transfusions when anæmia is intense and symptoms of shock occur, but these are risky unless an expert in blood grouping is available. The risk is greatest during the acute stage, and the procedure should never be lightly undertaken.

for some days after disappearance of the hæmoglobinuria. Granular *débris* and abundant tube casts are present in most cases. There may be a few red blood cells, but the condition is essentially one of hæmoglobinuria, not hæmaturia. There may be either polyuria or anuria.

Spleen. This has already been enlarged in most cases, sometimes it shrinks temporarily at the onset.

Cardio-vascular System. The pulse is weak, rapid, and of low tension ; heart failure due to toxæmia and anæmia is a frequent cause of death.

Nervous System. There is a feeling of prostration with anxiety and restlessness. The mental condition is usually clear.

Diagnosis

Most of the cases occur in places where the disease is so well known that the diagnosis is often made by the patient before the arrival of the doctor. In other cases the history of residence in a highly malarious area and the sudden change in the colour of the urine are highly suggestive.

Hæmaturia is easily distinguished by microscopical examination of the urine which is found to contain abundant red blood corpuscles.

Malaria with Bile-stained Urine. This is distinguished by spectroscopic examination of the urine or by the simple test of immersing a piece of white blotting paper for a few minutes in the urine. The staining due to bile is yellow or greenish-yellow, that caused by blood is reddish. There is less albumin in the urine and far more parasites in the blood in cases of " bilious " malaria.

Quinine Hæmoglobinuria. This is rare ; there is usually a history of previous attacks in conditions in which malaria can be excluded.

Paroxysmal Hæmoglobinuria. This is also rare and there is usually a history of previous attacks. Fever, rigors and vomiting are less pronounced.

Yellow Fever and Leptospiral Infections. In these the condition is one of hæmaturia.

Prognosis

This depends on the severity of the attack, the age and general condition of the patient, and the treatment.

The average mortality ranges from 10 to 40 per cent. in various localities. Hyperpyrexia, suppression of urine, deep jaundice, great prostration, profound anæmia, hiccough and persistently recurring paroxysms are unfavourable features. Relapses occur in about 10 per cent. of the cases. Later attacks are frequent.

Treatment

In spite of the fact that the disease is caused by malaria parasites, quinine and mepacrine are not recommended during the attack. The

porarily resident in the tropics will no longer suffer from black-water fever but with our interference with natural processes of acquiring immunity amongst indigenous peoples we may expect an increase in the amount of black-water fever in natives of the tropics.

The measures already described for the prevention of malaria must always be carried out : these will almost invariably eliminate black-water fever even when they are not completely successful in controlling malarial infection. If malarial infection still persists in a locality, every attack must be treated by a systematic course of chemotherapy ; irregular and haphazard treatment has been responsible for most of the cases of black-water fever. Clinical prophylaxis must be regular and continuous when it is carried out.

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Nevertheless, if circumstances are favourable and suitable blood is available, a continuous intravenous blood drip may be a life-saving measure and should be employed early in the course of treatment.

The addition of calcium lactate to the alkaline transfusion fluid is recommended by some physicians.

For vomiting and hiccough gavage followed by a dose of 10 minims of 1 in 1,000 adrenaline can be employed.

Phenobarbitonum (luminal) is valuable for restlessness ; it has been claimed to have a specific action on the disease itself, but claims for the efficacy of any drug should be received with great caution because of the impossibility of estimating how severe any case or group of cases would have been if the drug had not been used.

Antipyretics are harmful : hydrotherapy is the best treatment for hyperpyrexia. Alcohol should not be given except to addicts who are likely to suffer from its withdrawal.

The use of irritant purgatives such as calomel and jalap must be avoided. In cases of suppression the application of hot fomentations, kaolin poultices or dry cupping to the loins, high irrigation of the colon with warm saline and intravenous injections of 10 per cent. glucose (50 c.c. at a time) may turn the scale and produce a flow of urine.

Caffein citrate in doses of 2–3 grains twice daily is helpful.

Treatment During Convalescence. Complete rest must be insisted on for some days because of the tendency to heart failure. The diet should be generous and well supplied with vitamins. A course of iron and arsenic is started as soon as the patient begins to take solid food.

As soon as the patient has recovered from the acute condition a curative course of mepacrine and proguanil is given. The initial dose of mepacrine given should be small and tentative—0·01 gm. This is doubled every four hours till 0·08 gm. is reached, after which a full loading dose of mepacrine is given for twenty-four hours followed by the course of curative proguanil recommended in the section on treatment of malaria. At the end of the treatment a regular prophylactic proguanil routine should be instituted. If persisted in all fear of future relapses will vanish. If the patient has neither the will nor the intelligence to carry this out he should be invalided and be given no opportunity to return to a malarious country. When a patient who has had black-water fever goes to a cold country he should carry on with his daily proguanil until he has become reacclimatised to the cold.

Prevention

This is the same as for malaria. The disease is becoming much less frequent now that malaria control is being carried out more extensively ; it has completely disappeared from many places which once were notorious for its prevalence.

The time is rapidly approaching when the European who is tem-

unknown. The sporadic form is slightly milder and more chronic ; it occurs over wide areas in the southern Sylhet Valley of Assam, in Lower Bengal and Bihar, also in the easterly portions of the United and Central Provinces (*see* Fig. 12). It also occurs in Madras City and a few restricted areas of that province. The affected areas have a high degree of humidity and a minimum mean temperature not below 50° F., and in the Sudan it also has a close relationship to high humidity. In China it is prevalent from Manchuria and Peking in the north down to the Yangtse-kiang River and in Canton in the south. Both here and in India its distribution corresponds with that of certain sand-flies in which the parasite can develop. A few cases have also been met with in Brazil, Bolivia and in Argentina. Some of these were detected by finding the leishmania in the liver by post-mortem viscerotomy for the diagnosis of yellow fever.

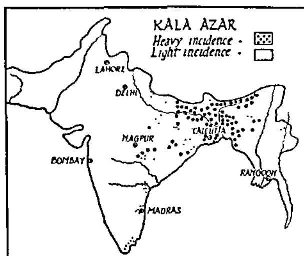


Fig. 12. Map of Kala-azar incidence in India.

The Infantile or Mediterranean Type of Kala-azar is also caused by the *L. donovani*, but it differs in some respects from the Indian form, especially in its age incidence and epidemiology. It is met with all round the Mediterranean basin, including Palestine, Turkey, extending up into Russia, Turkestan, Greece, Yugoslavia, Bulgaria, Italy, Southern France, Spain and Portugal, and all the north.coast of Africa and in the basin of the Blue Nile in the Sudan. The great majority of cases occur in young children, and only a few in adults. Throughout the Mediterranean area of infantile kala-azar a high rate of infection in dogs has been recognised in recent years. S. Adler and O. Theodor obtained infection of 100 per cent. of the sand-fly, *P. perniciosus*, in Malta by feeding them on infected areas of the skin of dogs, especially in September, when most infections are believed to take place, with an incubation period of about six months.

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In 1896–97 L. Rogers investigated the disease in the Nowgong district of Assam, where the epidemic produced such an appalling mortality that there was a decrease of 31·5 per cent. in the population in the decade 1891–1900. He regarded the disease as a form of epidemic malaria, because of finding malarial parasites in about 80 per cent. of the victims. At that time it was not known that a similar percentage of the general population harboured malarial parasites in the localities where the investigation was carried out. Rogers described the disease and showed the infection to be a house or site one; and that the spread on tea estates and up the Assam valley could be controlled by moving affected villages and coolie lines to new sites.

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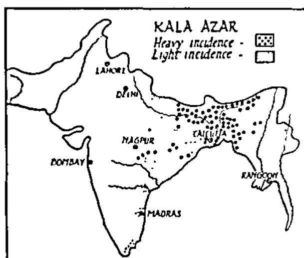


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the sand-flies, owing to the fact that the people slept on the ground floor.

R. Knowles, L. E. Napier and R. O. A. Smith then caused a number of laboratory-bred *Phlebotomus argentipes* to feed on kala-azar patients. In the first experiments they found flagellates in large numbers by the third to the fifth day after feeding, whereas no parasites of the kind were found in 811 control flies, or in 47 flies which had fed on



FIG. 13. *Phlebotomus argentipes*, showing pharyngeal infection with *Leishmania donovani*. (After Shortt, Barraud and Craighead.) F. Flagellate near anterior extremity of pharynx. F2. Flagellates anterior to crinkly portion. F3. Flagellates breaking free from main mass of growth. F4. Massive growth of flagellates at posterior end of pharynx.

patients who were not suffering from kala-azar. S. R. Christophers and H. E. Shortt confirmed and extended this discovery by keeping the fed flies alive for longer periods and obtaining massive infection of the mouth parts with flagellates which must inevitably be injected into persons bitten by such sand-flies (*see* Fig. 13). In China the *P. sergenti* and *P. chinensis* were similarly infected by biting kala-azar patients

much smaller numbers in other organs. Numerous small immature bodies are found in the large endothelial macrophage cells of the reticulo-endothelial system more particularly; these rupture and discharge the bodies into the circulation. In the blood-stream they are seen as larger ovoid bodies with rounded macronucleus and rod-shaped micronucleus inside a thin-walled capsule; these are often taken up by the polynuclear and large mononuclear leucocytes. Being present in the peripheral blood they are liable to be swallowed by biting insects. This human stage of the organism is illustrated by Nos. 2 to 4 in the Coloured Plate. They stain well by the Leishman method, by which they were first discovered. They are readily found in smears made from material aspirated by spleen, liver or bone-marrow puncture.

Cultures were first made in Calcutta by the simple plan of adding spleen-puncture fluid to a little citrate of soda solution in a small sterile test-tube and incubating at a temperature kept below 70° F. with the aid of ice. Neutral blood-serum agar is now generally preferred and the organisms develop in the water of condensation of such media. Within twenty-four hours the parasites multiply by division, first of the micronucleus, then of the macronucleus, after which the organism splits into two. At the same time they become larger and develop a blue-staining protoplasm. By the third day they elongate, and a flagellum grows out of the micronucleus. Division now takes place so rapidly that they soon form large rosettes with the flagella in the centre. This flagellate stage is never seen in the human body, and, as a neutral or slightly acid medium and sterility are essential for successful cultivation, it is unlikely that parasites which are discharged into the lumen of the bowel can undergo development into the flagellate form. Gavrilov and Laurencin have cultivated leishmania in the tissues of embryo hamsters and observed penetration of the cells by the flagellates and their development into leishmania forms. The organism has since been grown by inoculation into the yolk-sac of embryo chickens and incubating at 39° C. and by Hawking in tissue cultures of hamster spleen and rabbit serum with the formation of masses of flagellates and invasion of uninfected spleen cells.

Development in Sand-flies

Patient work, especially in India, at length supplied the key to the solution of the problem of the transmission of kala-azar. L. E. Napier found that few cases originated in the crowded Indian centre of Calcutta, but many in the one-storied houses in the suburbs. A fly census showed that far more sand-flies occured in the latter area. Serological tests by R. B. Lloyd showed that the sand-flies in the city houses had fed on cattle which are kept on the ground floor, and that the people living in the upper stories were not bitten by the insects; whereas in the kala-azar areas human blood was often found in

Animal Infections. In addition to the frequent natural infection of dogs in China and in the Mediterranean area, but very rarely in India, as already mentioned, in Turkistan gerbils, *Rhombomys opimus*, frequently suffer from cutaneous leishmaniasis, and a bullock has been found naturally infected with the organism of kala-azar in Assam. Mice, monkeys and cats can be infected artificially.

Prophylaxis. In the 1897 report of the writer evidence was brought forward to show that kala-azar is essentially a house or site infection, so that the best means of controlling the spread was by isolating the infected and moving the remaining healthy persons from their lines or villages to a new site a few hundred yards away. J. Dodds Price and the writer reported in 1914 the success of this measure in stamping out kala-azar from ten badly-infected tea estates with a total population of 6,727 persons during a period of eighteen years. In two places in which the plan was not adopted the infection continued throughout that period, so that there was an effective control test. A similar measure also proved effective in dealing with outbreaks in Assam villages.

In recent years intravenous injections of antimony preparations have been used on a large scale to cure kala-azar patients, and thus reduce the number of persons who harbour infection. Thus, T. McCombie Young in 1923 reported the recovery of 80 per cent. of 80,000 patients in Assam villages against 5 per cent. in 1896, with the result that the 1921 census showed no fall in the population in the affected areas. More recently the extensive use of pentavalent antimony compounds by the Assam Government has been followed by a great reduction in kala-azar cases. In Italy a steady decline in the incidence of the infantile form followed systematic treatment with tartar emetic and other forms of antimony. The remarkable results obtained by treatment with neostibosan described below have enabled L. E. Napier and Das Gupta to stamp out the disease from a group of villages near Calcutta by systematic searching for and treating all the kala-azar cases. By these means the number of cases found yearly was reduced from 121 and 127 respectively in the first two years' work to only twelve and three in the fifth and sixth years, followed by the disappearance of the disease for several years. This formerly deadly disease can therefore be eradicated by the efficient use of such measures. In the Sudan R. G. Archibald and H. Mansour advised an intensive yearly inspection of the people in May and June to detect and treat as many cases as possible before the July to October infective season. Methods based on the prevention of sand-fly transmission may also prove to be of practical value, although, unfortunately, these insects are small enough to get through the mesh of any mosquito curtain which would be bearable in steamy Bengal, and few of the people in the affected areas can afford the luxury of effective nets. R. O. A. Smith found that *P. argentipes* breed within twenty yards of a house

and hamsters were infected through their bites. In both countries the distribution of kala-azar cases closely corresponds with the incidence of those insects. In the case of the Mediterranean infantile kala-azar Adler found *P. perniciosus* to be the principal carrier in Sicily and in the Sudan *P. langeroni* was incriminated as the carrier by Kirk. Napier has infected *P. argentipes* by causing them to feed on the dermal lesions of recovering kala-azar patients in Calcutta.

In the meantime it had been discovered that the Chinese hamsters, *Cricetulus griseus*, can be readily infected by the injection of the human stage of *L. donovani*, and in 1930–33 several workers very occasionally succeeded in infecting these animals through the bites of infected sand-flies with the very long incubation period of a year or more. In 1940 further progress was made when R. O. Smith and others reported that *P. argentipes*, fed on raisins after a preliminary feed on the blood of a kala-azar patient, frequently developed blockings of the œsophagus by masses of flagellates, and that such blocked sand-flies readily infected hamsters with far shorter incubation periods than had previously been observed.

In China two children developed kala-azar nine and ten months respectively after transfusion with the blood of their infected mother.

It was not until 1942 that healthy volunteers were infected through the bites of sand-flies previously fed on kala-azar patients; the conditions were such that naturally acquired infections were excluded. In three of the cases infection was found three to five months after repeated feeds. The possession of effective drugs against the disease enabled these crucial tests to be carried out by Swaminath, Shortt and Anderson without risk to the volunteers.

Predisposing Causes. In 1897 L. Rogers showed that the Assam epidemic of kala-azar originated in the spread of the disease to the Garo Hill district of Assam across the wide Brahmaputra River from Eastern Bengal at a time when an epidemic of malaria was raging in the latter area. The parasite of kala-azar had not then been discovered, so he regarded the Assam outbreak as epidemic malaria. On the discovery of the Leishman-Donovan body, in 1903, it became evident that the Bengal malaria epidemic had only predisposed to the spread of kala-azar to Assam, much as the 1918 influenza epidemic predisposed to a recrudescence of kala-azar in the eastern portion of the Brahmaputra valley. It is therefore of interest to note that in 1941 R. O. A. Smith and I. Ahmed, as the result of an inquiry into the prevalence of malaria and kala-azar in Bihar, immediately to the west of Bengal, reported that localised epidemics of malaria had been followed by a considerable increase in the incidence of kala-azar, and although very few of the kala-azar patients showed malarial parasites in their blood, as had been noted by previous workers, they thought that malaria probably caused the sudden increase of the cases of kala-azar by lowering the resistance of the patients.

sometimes extends several inches below the costal margin even when the patient has only recently begun to complain of fever. There are, however, rare exceptions, such as were described by J. Dodds Price, who was able sometimes to recognise the disease clinically before evident enlargement of the spleen was present. The organ as a rule is hard at this stage, and it may even give rise to a visible protuberance, easily seen and felt through the emaciated abdominal wall. The enlargement is great, as is shown by the fact that the spleen reaches to the navel or below in over 60 per cent. of cases of over three months' duration; not infrequently it may even reach to the level of the anterior superior spine of the ilium.

The *liver* also becomes enlarged after three to six months' fever, and reaches to one to four fingers' breadth below the costal margin in the nipple line. The edge is sharp and there is no pain. The enlargement is usually less than that of the spleen, but the reverse may be the case, and the increase in size is usually greater than is seen in chronic malaria; the organ could be felt below the ribs in 75 per cent. of the sporadic Bengal cases. It may occasionally be very hard owing to cirrhosis of the type described by the writer as intercellular, the increase of fibrous tissue being found within the lobules around the capillary vessels. The surface is quite smooth in typical cases, and fatal ascites may accompany the cirrhosis.

The *fever* of kala-azar runs a very variable course, but a characteristic feature is the double remittent type which was first described by the writer; this is not always present, but is common when the fever is of the remittent type (*see* Fig. 14, Chart 3). It consists of two or even three distinct rises and falls in the twenty-four hours, the last of which commonly occurs late in the evening or at night, and so may easily be missed. It is necessary to take the temperature every four hours, otherwise this striking feature may be overlooked. In any fever which could be kala-azar the presence of this type of curve is practically diagnostic of the disease. Another rather typical temperature curve often seen in kala-azar is the low continued type, in which the temperature never falls to normal, and does not vary more than 2° F. during the day or night for some days, yet never rises more than 2 or 3 degrees above the normal. At other times there is an intermittent fever with no characteristic feature, but if the temperature is taken four-hourly there may be a typical second rise. In the early stages high-continued or remittent fever is often seen (*see* Fig. 14, Chart 1). This is commonly mistaken for typhoid, and in most of the typical cases of kala-azar in Europeans there was a history of an attack of "typhoid" which was said to have occurred a short time before the characteristic enlargement of the spleen with persistent fever caused kala-azar to be suspected. Even in the typhoid-like stage the double rise is sometimes seen; this should arouse suspicion and so lead to an early diagnosis of kala-azar. In other cases the fever comes

or cattle-shed, but spraying those sites did not reduce the insects in the houses, so they advise attacking the adult insects within the houses by sprays or fumigation as in the case of mosquitoes (*see* p. 49).

In the infantile Mediterranean kala-azar detection of the close association of the disease with infected dogs led to the destruction of the great majority of them in Canea, Crete, followed in a short time by a much lower incidence of human kala-azar.

Spraying the insides of the walls of houses and out-houses in Greece and Italy with D.D.T. has been reported by Hertig to be effective for several months against the bites of sand-flies. Spraying of the walls of mud houses and of spaces on stone walls where the flies are found, is also of value. The range of flight of the insects is reported to be *only from 75 to 200 yards.* In the South of France dry years have been found to be unfavourable and wet ones favourable to the prevalence of sand-flies.

CLINICAL DESCRIPTION

In the epidemic form, now happily greatly reduced in Assam, kala-azar was easily recognised by its occurrence in large numbers of people in one place. In its more widespread sporadic form it is very liable to be mistaken for typhoid in its early stages, and for chronic malaria when it has lasted for some months, but nowadays it can be differentiated fairly easily by modern methods of diagnosis mentioned later (p. 74). It will simplify matters to describe the fully-developed disease first, and to return to the more difficult early stages which are so important from the point of view of diagnosis.

The incubation period varies from a few weeks to four or more months.

General Appearance in Typical Cases. The chief feature of the typical kala-azar patient is his great emaciation contrasting with the protuberance of the abdomen, which is due to the great enlargement of the liver and spleen ; usually there is a prominence of the superficial abdominal veins, and the face often has a peculiar dusky appearance. A large proportion of the cases occur in children, and very often there is more than one victim in the family, whose members are attacked one after another. There is persistent fever, although after a time the patient is often unaware of it. Anæmia is not so constant or pronounced as in malaria, but in long-standing cases it develops together with œdema of the feet ; sometimes there is also ascites. The patients rarely die directly of the disease, but usually from secondary bacterial infection, such as sepsis, pneumonia or dysentery, and in children cancrum oris often ends the scene. The lingering nature of the disease and its very high mortality rendered it one of the worst of human maladies.

The great enlargement of the *spleen* is the most striking objective feature, it may be one of the first symptoms ; the edge of the spleen

pneumonic complications in the later stages may be accompanied by a high continued fever and rapid downhill course.

Fever in the Early Stages. The recognition of kala-azar in an early stage may be very difficult, in striking contrast with the ease with which the diagnosis is made in the later ones. The onset of the disease can be studied best in European patients. The temperature is usually of a high remittent type.

The most common tropical disease for which early kala-azar may be mistaken is malaria, for the spleen may become enlarged within a few days of the onset of fever in a case of kala-azar. A four-hourly temperature chart will usually allow malaria to be excluded by the absence of the typical curve of malignant tertian or of single infections with the benign tertian and quartan malarial fevers. In the typhoid-like early kala-azar charts the remittent type of fever is commonly replaced by a low intermittent type after two to four weeks, in contrast with the subnormal temperature of convalescing typhoids.

Blood Changes. These are very characteristic and of great diagnostic importance. The anæmia steadily increases as the disease progresses, but is not so severe or so rapidly developed as in chronic malaria. In about half the cases the red corpuscles fall to between 2,500,000 and 4,000,000, and in only one-sixth do they decrease below the lower figure. The most striking feature is the degree of leucopenia, and especially the great reduction in the ratio of the white to the red corpuscles, which should normally be about one white to 750 red. In a series of typical advanced cases verified by spleen puncture in Calcutta the leucocytes were below 3,000 in no less than 94·8 per cent. of the cases, they were below 2,000 in 72·8 per cent., and they were 1,000 or less in 42 per cent. Further, in 70 per cent. the ratio was under 1 white to 1,500 red, viz., less than one-half the normal proportion, and in 50 per cent. the ratio was under 1 to 2,000. The last figure is almost diagnostic of kala-azar, and a ratio of 1 to 1,500 or less is highly suggestive, as apart from cases of kala-azar it was only found in a very few exceedingly chronic cases of malarial splenomegaly which were of several years' duration, and therefore unlikely to be confused with kala-azar, which does not as a rule last nearly as long.

The differential leucocyte count is equally important. The essential change is a great reduction in both the total and relative numbers of the polymorphonuclear white corpuscles, with a relative, but not an actual, increase of the mononuclears both small and large; the eosinophiles are so greatly reduced that frequently none are found in a count of 500 white cells. The importance of these changes is brought out most clearly by estimating the number of polymorphonuclears per cubic millimetre, which normally should be about 5,000, whereas in a series of seventy-six kala-azar cases they only exceeded 3,000 in 5 per cent. of cases; they were below 3,000 in 84 per cent., and below 1,000 in no less than 60 per cent. The prognosis is bad in proportion to the

on gradually, accompanied by steady enlargement of the spleen. The persistence of fever of varying types and severity is a striking feature of the disease, and before the antimony treatment was discovered it was common for charts of from six months to a year to be recorded in

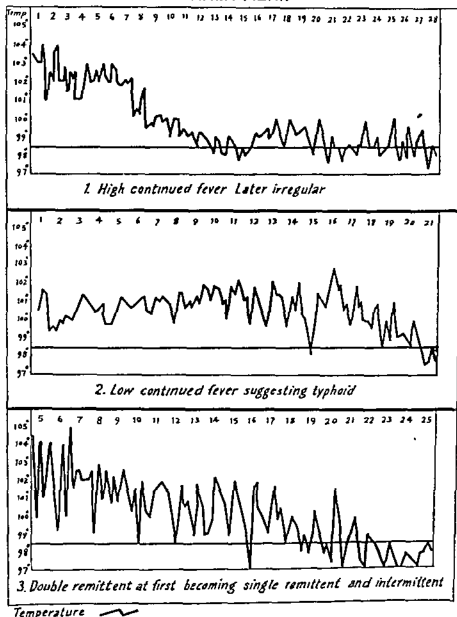


Fig. 14. Temperature charts of kala-azar.

hospital cases without a single day's complete freedom from rise of temperature, although the patients might sometimes be quite unaware of the existence of fever. When the fever is of a remittent type the patients lose weight steadily and go down hill, but when it falls to a low intermittent type, with daily rises up to about 100° F., weight may be gained and general improvement take place. Septic and

Circulatory changes, including low blood pressure, hæmic murmurs and rapid pulse, are common ; the latter is an aid in the differentiation from typhoid fever.

The **digestive system** is little affected ; the patient retains a clean tongue and a remarkably good appetite as a rule, but in the late stages he is very liable to suffer from *diarrhœa* or *dysentery*.

Nasal and oral infections have been recorded in India, with



Fig. 15. Kala-azar Dermal Leishmaniasis. (After Napier and Das Gupta.)

leishmania in the secretions, from which hamsters have been infected by intraperitoneal injections. Polypi have been met with on the nasal septum in Brazil.

Post-Kala-azar Dermal Leishmaniasis. This condition was first described by U. N. Brahmachari in Calcutta and closely studied by L. E. Napier and C. R. Das Gupta on the basis of 394 cases. Three-fourths of the cases are met with in patients who have recovered from the febrile form of kala-azar, a history of which was obtained in 82·5 per cent. of cases. The most typical condition is the appearance of nodules on the skin, as shown in Fig. 15, in which numerous *L. donovani* parasites can be found in macrophage cells. This type may be mistaken for nodular leprosy. Leishmania-containing nodules have also been found in the tongue. Depigmented areas and erythematous or butterfly rashes are also common, together with the

reduction in the total polymorphonuclears : this is a measure of reduced resistance to the bacterial infections, which cause the fatal termination of most cases of kala-azar. An extreme reduction of the polymorphonuclears may also occur in agranulocytosis, which has been reported in rare cases to have followed the antimony treatment of kala-azar in China.

In advanced cases in which there is great anæmia the coagulability of the blood may be reduced ; for this reason spleen puncture should not be performed in such cases unless the blood is found to clot within five minutes in Wright's tubes. Fatal intra-abdominal hæmorrhage has resulted from failure to test the coagulability of the blood. An injection of horse serum will sometimes raise the coagulability to a safe degree. The sedimentation rate of the red corpuscles was found to be increased in all cases by H. Chung. The alkalinity of the blood is also reduced in kala-azar. Blood sugar and lævulose tolerance are reduced.

Progress and Terminal Complications. The fever of kala-azar may continue with varying degrees of severity in untreated cases for many months. The average duration of the disease from first to last in 193 tea-garden cases observed in the Assam epidemic long ago was 7·4 months, but it may occasionally be as long as several years in the sporadic form. E. Muir found that the duration was seldom more than twelve to fifteen months in Bengal. There is also some evidence that infection with the Leishman-Donovan bodies may exist without obvious symptoms. The primary disease is rarely the direct cause of death, which is almost always due to one of the following complications.

Septic infections are by far the most frequent complications. In the case of children the most common form is *cancrum oris* ; this may cause extensive sloughing away of the cheek. This complication has also been observed in monkeys infected with kala-azar. These infections usually occur in a late stage when extreme leucopenia is present, and under such circumstances the septic infection only produces a slight increase of the white corpuscles, and not an actual leucocytosis ; but in the few cases in which the white corpuscles rise up to or above the normal, recovery may take place. P. L. Fan and A. V. Scott reported benefit from blood transfusions. Penicillin intravenously and locally every three hours is of great value in *cancrum oris*.

Pneumonia is a frequent complication : leucocytosis as a rule only occurs in early cases, but when there is a pronounced leucocytosis there may be prompt recovery from the primary disease. Observations of these recoveries led the writer to attempt to increase the leucocytes by the use of staphylococcus vaccines, etc., with only occasional success.

Phthisis also occurs as a very serious complication not amenable to treatment, as antimony preparations may aggravate the condition. A tendency to hæmorrhage used to be seen in many cases towards the end of the disease, most commonly in the form of purpura ; meningeal hæmorrhage or bleeding from *cancrum oris* also occurred in some cases.

the numerous leucocytes found in the terminal part of straight-ended films in accordance with Shortt's technique ; this is worthy of trial before proceeding to puncture an organ.

Lymph-gland puncture has also yielded 60 per cent. or more of positive results in the Mediterranean infantile kala-azar. Kirk and Sati in the Sudan found leishmania in 31 of 54 cases by examining scrapings from small superficial papules and ulcers of the skin.

Spleen Puncture. Spleen puncture, especially if combined with culture, is the surest method of diagnosis, and can be carried out safely in patients who are not very anæmic or œdematous if the following precautions are taken. Calcium chloride or lactate is given in 30-grain doses half an hour before, and in patients in hospital also on the previous evening. The patient should be lying down, the skin is cleansed, and then the site of puncture is sterilised by tincture of iodine or a drop of carbolic acid at a spot an inch below the costal margin and in the middle of the breadth of the spleen. An assistant standing on the right of the patient should fix the organ with his hand placed below and to the right to prevent it moving. A stout needle 1½ inches in length is first made to penetrate the skin into the subcutaneous tissues obliquely, and is then plunged firmly into the spleen in a backward and upward direction. The interior of the syringe should be dry, and the piston should be withdrawn rapidly for an inch, two or three times if necessary, until a small drop of blood appears in it. The patient should be kept in bed for a day, with a tight abdominal bandage if in hospital, and out-patients should lie still for half an hour and be watched for another hour before being allowed to depart.

Although the operation is safe in skilled hands, it is necessary to remember that there have been a number of fatalities, so spleen puncture should not be undertaken light-heartedly by the inexperienced. Some regard liver puncture as safer, but the parasites are less likely to be found. A drop of the blood is smeared on a clean slide and stained with Giemsa's or Leishman's stain.

Sternal or Tibia Puncture, to enable the cancellous bone marrow to be examined for leishmania, has been advised by workers in several countries as simpler and safer than spleen puncture, but it gives fewer positive results.

The Aldehyde Test has largely replaced spleen puncture in the investigation of chronic fevers suspected to be kala-azar as it is simpler and safer. Clear serum is obtained by withdrawing about 5 c.c. of blood from an arm vein of the patient and allowing it to clot. To 1 c.c. of the serum, in a small test-tube, 2 drops of commercial formalin solution are added. A positive reaction is indicated by immediate white opacity followed by the development of a firm white gelatinous mass within half an hour. Jellification has no significance in itself : the jelly must be white, like blancmange. The reaction corresponded with spleen puncture results in 84·7 per cent. of cases ; it diminished or

less frequent verrucose, papillomatous and xanthomatous types. L. E. Napier has demonstrated the same organism in the skin in many cases without evident lesions, and he has infected sand-flies by feeding on such patients, who may thus prove to be a source of infection very difficult to detect. These conditions will clear up under prolonged antimony treatment; they are most likely to occur in kala-azar patients who have been insufficiently treated. They appear to be rarely met with in Assam, but are not infrequent in Madras. R. Kirk reported a primary cutaneous infection from the Sudan. In one reported case the cornea was also involved but improved under treatment.

DIAGNOSIS

This has to be considered primarily from the clinical point of view, because most of the practitioners in kala-azar infected areas are beyond the reach of well-equipped laboratories. Most of the patients come for treatment with the disease fully developed, when an *experienced doctor can usually make the diagnosis at a glance.* The main difficulty is to decide between kala-azar and chronic malaria with enlarged spleen: the diagnosis can usually be made by observation of the patient for a week, during which 20–30 grains of quinine are given daily. If the fever persists in spite of this treatment, malaria can be excluded, and doubt as to the nature of the disease will no longer exist, except in a few places where undulant fever is also prevalent; this can be distinguished by the macroscopical agglutination test with dead cultures. For practical purposes the simple quinine treatment test generally suffices, but where the circumstances permit it should be supplemented by spleen, liver or sternal puncture or preferably the aldehyde test, carried out as described below. In the less frequent cases in which the patient comes under observation during the first bout of fever the clinical diagnosis is much more difficult and the disease is then most likely to be confused with typhoid. A slow pulse will be much in favour of the latter, and a quick one of kala-azar. A high-continued fever, without the appearance of the double daily remission, nearly always means typhoid, as does severe prostration, the typhoid condition and abdominal symptoms other than those due to enlarged spleen. The milder types of typhoid with remittent fever seen so often in children are less easy to distinguish, especially as the slow pulse is not a pronounced feature of typhoid in the young. In these cases early blood culture or a succession of Widal tests may be necessary before a certain diagnosis can be made; the same remarks apply to undulant fever, which fortunately is very rare in the kala-azar areas of India, but prevalent in the Mediterranean area.

Examination of Blood Films for L. donovani. Degrees of success varying from 1 to 39 per cent. have been reported in the diagnosis from the use of this method. The parasites should be sought for in

syphilis may fail to respond to antimony treatment until that complication has been cleared up. These trivalent antimony salts have been replaced by the more efficient pentavalent ones described below.

Neostibosan is the most efficacious drug in kala-azar as shown by prolonged trials in Calcutta by Napier. It is given by an intensive course of ten daily intravenous or intramuscular injections of 0·2 gm. for the first and 0·3 gm. for subsequent doses. In cases followed up complete cure was obtained in 90 per cent., 6 per cent. relapsed and *only 2·30 per cent. died; late cases did quite as well as early ones.* Napier has also cleared up with this drug 150 cases of the chronic dermal form of late *L. donovani* kala-azar infections.

In the Mediterranean infantile form of kala-azar better results are obtained with neostibosan than with other antimony preparations.

Urea-stibamine of U. N. Brahmachari is of value in doses of 0·1 gm. increased by 0·05 gm. at a time up to a maximum of 0·25 gm. with a total quantity of 2·6 gm. in twelve doses in the course of thirty-two days in adults.

Sodium Antimony Gluconate (solustibosan, stibatin) is a very active preparation, which has the advantage of being little toxic and almost painless by intramuscular injection and consequently it is specially serviceable in the treatment of children. It can also be given intravenously in adults up to a total of 3 gm. per 100 lb. body-weight in 1·4 c.c. doses of a 4 per cent. solution, on alternate days with relatively smaller doses in children. This drug is less efficacious than neostibosan.

Diamidines. In view of the resistance of occasional cases of kala-azar to antimony it is important to have alternative methods of treatment. Liverpool workers have provided this in the form of 4 : 4′-Diamidino stilbene which has a marked effect in eradicating the infection of hamsters. Good results have now been obtained in the human subject by eight daily intravenous doses of 1·0 mg. per kilo. In the Sudan form. which is less amenable to antimony than Indian cases, 86 per cent. showed *immediate recovery* without any relapse within six to seven months in those that could be followed up. In Calcutta good results have been obtained from intravenous injections of diamidino stilbene, or stilbamidine as it is now called, but intramuscularly it proved to be very painful. From 10 to 12 or up to 15 daily doses were given, beginning with 0·025 gm. in adults and increased by 0·010 daily according to the reactions up to a maximum of 0·1 gm. (0·001 gm. per lb. body-weight). In small children the first dose should be 0·010 gm. gradually rising to 1 mg. per lb. body-weight. The reactions include temporary great fall in blood pressure. However, after the use of stilbamidine cases of neuropathy, such as paræsthesia and trigeminal anæsthesia, have been reported two to eight months after the treatment and gradually improving after some eighteen months. This drug should therefore be used only in cases resistant to neostibosan.

disappeared with the recovery of patients under the antimony treatment, but it is usually absent during the first three months of the illness, and so cannot be relied on in the early stages. A strongly positive reaction may be accepted as diagnostic of kala-azar.

Serum-antimony Test. R. N. Chopra has found that the pentavalent antimony compounds, when added to kala-azar serum, produce a precipitate much in proportion to their therapeutic efficacy; this reaction runs closely parallel with the aldehyde one. It appears earlier, but is less reliable than the formalin test. R. B. Lloyd found that both reactions depend on an excess of altered euglobulin and a decrease of serum albumen in the blood in kala-azar, so that the globulin-albumen ration rises from 0·66 to over 2·9. It falls rapidly with the antimony treatment, so this may furnish a serological control of recovery very similar to the Wassermann test in syphilis.

Prognosis. This has been converted from one of the most gloomy in medicine to one of the most promising by the discovery of the curative action of the antimony and other compounds, except in very debilitated and dropsical cases, in which usually there is an extreme degree of leucopenia.

TREATMENT

Historical. In 1913, Vianna and Machado, in Brazil, reported the cure of cutaneous and oral forms of Leishmaniasis by intravenous injections of tartar emetic. Reports of this success were naturally followed by the trial of the drug in kala-azar, and in 1915 di Cristina and Caronia, working in Sicily, recorded the cure of several cases of infantile kala-azar with tartar emetic injections. In the same year similar good results were obtained by L. Rogers and by E. Muir in kala-azar of Bengal. Subsequently various pentavalent antimony compounds were introduced, and were found to give more rapid results than the tartrates.

In decisions regarding suitable doses of all the following drugs the body-weight of the patient must be taken into account. The doses prescribed are for persons weighing about 100 to 110 lbs. In œdematous patients an allowance must be made for the additional weight due to this condition.

The sodium and potassium tartrates of antimony are toxic and irritant salts which are given intravenously in sterile watery solutions. The initial dose should be ½ grain in 1½ c.c. of the 1 per cent. solution, and it may be increased by 0·5 c.c. each week up to a maximum of 2 to 2·5 grains; the injections may be given every two or three days, as long as no toxic symptoms or excessive reactions occur. If any of the fluid escapes into the tissues around the vein intense pain and a hard indurated sterile inflammatory swelling will ensue.

In children the dosage should be in proportion to the weight of the patient. Cases of infantile kala-azar complicated by congenital

CHAPTER III

AFRICAN TRYPANOSOMIASIS OR SLEEPING SICKNESS

Definition. African trypanosomiasis is a chronic disease of tropical Africa caused by protozoal parasites, *Trypanosoma gambiense* and *rhodesiense*, which are transmitted by tsetse-flies. There is irregular chronic fever and lymphadenitis in the earlier stages. Later there is somnolence and other nervous symptoms due to the involvement of the central nervous system, and unless it is efficiently treated, the disease usually terminates in death after a long course.

Historical. The advanced sleeping-sickness stage of trypanosomiasis was known in West Africa for a century before 1901 when Forde found in the early febrile stage a parasite in the blood, which Dutton identified as a trypanosome. In 1900 the outbreak of epidemic sleeping sickness on the northern border of Lake Victoria Nyanza afforded opportunities for research by which Castellani found trypanosomes in the cerebrospinal fluid of cases and David Bruce found trypanosomes in the blood of mild fever cases and followed them up to the development of cerebrospinal involvement with symptoms of sleeping sickness.

In Uganda the mode of infection at first was considered to be due to direct transmission of the trypanosome infection mechanically by the bites of tsetse-flies within two hours of their having fed on an infected subject. In 1909 Kleine in East Africa by means of experiments on monkeys with laboratory-bred tsetse-flies found that the trypanosomes disappeared from the guts of the fed flies but reappeared after twenty days in some of them, which then remained infective up to over sixty days. The cyclic development of the organisms in the tsetse-flies was thus established as the ordinary mode of infection.

In 1910 Stephens and Fantham recorded the development in rats inoculated with a virulent form of sleeping sickness met with in Rhodesia of about 5 per cent. of short forms with the micronucleus further forward than in the common form of the trypanosome. They regarded this as a new species, but Kleine and others regarded it as only a virulent form of the common species.

Geographical Distribution. The Rhodesian type of trypanosomiasis occurs as scattered endemic cases in the south of Tanganyika Territory, Nyasaland, Portuguese East Africa and Rhodesia, all of which border on the Nyasa Lake. The disease has also extended up to the south of Lake Victoria Nyanza and the S. Sudan, but the cases are not very numerous. The Gambiense variety is prevalent in an endemic form in West Africa from Senegal in the north to Angola in Portuguese West Africa in the south, and on the islands of the Gulf of Guinea, along the low-lying coast, and especially in the hot valleys

The Criteria of Cure. Insufficiently treated cases of kala-azar are liable to relapse. It must also be remembered that there are very rare cases of kala-azar which are uncontrolled by even the newer most active antimony preparations. A more common difficulty is to determine when a patient is cured, and when it is safe to discontinue the antimony injections. As the vast majority of cases are treated far from pathological laboratories, the clinical criteria may first be dealt with. The complete cessation of fever and its continued absence for a considerable *time is a favourable sign, if accompanied* by a substantial gain in weight approaching nearly to the normal. So also is disappearance of the spleen beneath the costal margin in cases in which it had not been enlarged much below the navel when treatment was commenced, or reduction by several inches when the organ originally was well below the level of the navel. Disappearance of the leucopenia with increase of the total leucocytes to the normal number or over also occurs in favourable cases. After recovery it is well to see the patient occasionally to detect and treat any relapse by a repetition of a full course of the most active antimony drugs.

The **Laboratory Tests of Cure** include the aldehyde reaction, which often becomes negative after recovery, but this is not a very reliable criterion. Of much more value is the performance of spleen or bone-marrow puncture with cultures. Absence of the parasite, both microscopically and after three weeks' culture, affords the most reliable evidence of a complete cure, although a simple microscopical examination cannot be relied on because of the scantiness of the organisms when the patient progresses towards recovery.

In **cancrum oris** penicillin, both locally and by injection, is very efficacious. When it is not available swabbing with permanganate of potash solution may be alleviative. The use of penicillin has also greatly improved the prognosis of pneumonic and septic complications of kala-azar.

The Technique of Intravenous Injections. With the patient recumbent a prominent vein at the elbow is selected, usually the median basilic. This is distended by pressure applied above the site by an assistant, or by a piece of pressure tubing or bandage looped round the arm, or, still better, by the air bag of a blood-pressure instrument. The vein is now punctured through the previously sterilised skin with a needle, which must be sharp, attached to the glass syringe containing the dose. It is essential to draw up a little blood into the syringe before injecting the dose to ensure that the needle is really in the vein, as any escape into the surrounding tissue produces acute inflammation. The pressure is now released, the dose injected slowly, and a little cotton wool and collodion applied after withdrawing the needle.

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metres of citrated vein blood and examining the layer just above the red corpuscles (*see* Fig. 1 of Coloured Plate 16-17).

Animal inoculations, when available, furnish a more delicate method of diagnosis, as the human parasites multiply greatly in the blood of rats or other ordinary laboratory animals, but rats must always be examined for their natural trypanosomes before being used for this purpose. The parasites can be cultivated on the N.N.N. blood-serum agar medium.

Laboratory Infections have been reported. In one case it was due to infected blood being sucked up in a pipette by a person who had ulcerated tonsils ; in two others it resulted from the contamination of fingers with infected blood ; cures were effected in all the cases.

The trypanosomes are also present in numbers in the enlarged glands which are so frequently found in all stages of the disease. By *puncture of the glands in the posterior triangle of the neck it is possible* to secure a fluid which is much richer in the parasites than the peripheral blood.

Relation of Trypanosomes to Tsetse-flies. In the first place, there is a close relationship between the distribution of *Glossina palpalis* and the common *T. gambiense* form of sleeping sickness, and also between *Glossina morsitans* and the virulent *T. rhodesiense* variety of the disease, but in the Nyanza district to the south of the Victoria Nyanza Lake another species of fly, *G. swynnertoni*, was found to be the carrier. *G. palpalis* is found only within a short distance of water, and it also likes shade, so that the forest-clad banks of rivers and lakes are its regular haunts, where both man and animals coming for water are liable to be attacked by the flies. The other two varieties are found much farther from water and are thus more difficult to avoid. In hot Northern Nigeria, T. A. M. Nash found a high mortality among glossina at maximum day temperatures of 100°–103° F., but a humidity of 80 per cent. with a temperature of 24° C. is favourable for keeping tsetse-flies alive.

There has been much discussion as to whether the tsetse-fly conveys the trypanosomes directly by mechanical transmission of parasites which adhere to the proboscis of the insect or whether a cycle of development of the parasites takes place in the alimentary canal of the insect. Both modes of transmission appear to occur under natural conditions. The direct method was for long thought to be the ordinary one before cyclical development in the insect was discovered. As early as 1899, L. Rogers found that infection with the trypanosomes of horse surra in India, due to *Trypanosoma evansi*, could be conveyed readily from an infected laboratory animal to a healthy one by the bites of horse-flies (*Tabanidæ*), but this direct transmission occurred only for a few hours after the insect had bitten an infected animal ; it never occurred after the lapse of twenty-four hours, so that the transmission was obviously only mechanical (*Proc. Roy. Soc.*, 1901). In

of the numerous large rivers draining the Congo basin. It extends east to the Southern Sudan, Uganda, and around the Lake Victoria Nyanza, including portions of Kenya and Tanganyika, and it caused very serious depopulation in the French and Belgian areas.

Incidence. In 1948 T. H. Davey gave the following estimate of the incidence of the disease. In Nigeria six million of the twenty-two million people are exposed to the infection. An examination of four million of them revealed an infection rate of 8 per cent. In half of Nigeria no cattle can be kept on account of trypanosome infections, resulting in lack of meat, milk and animal transport. On the Gold Coast 75 per cent. of the four million inhabitants are exposed to infection and the incidence varies between 1 and 50 per cent. Sleeping sickness is a major cause of mortality with rapid depopulation where the incidence is 13 per cent. or over. In Sierra Leone the incidence is only about 1 per cent. and the disease is under control. In Gambia there is an incidence of only 1 per cent. of a mild type. In the Anglo-Egyptian Sudan the disease is under control with under 100 cases and a few deaths. In East Africa in 1947 Buxton reported less than 2,000 cases and about 300 deaths in Kenya, Uganda and Tanganyika. In the Rhodesias, Nyasaland and Ngamiland about 100 cases and 10–20 deaths yearly. Much has therefore already been done to control trypanosomiasis in British-administered areas of Africa as the result of investigations during the last half century.

Ætiology. The causative trypanosomes belong to a class of protozoa which are parasitic in many species of animals in Africa and elsewhere ; they can be differentiated from one another with considerable difficulty, usually by means of animal experiments. They are elongated uniflagellate protozoa varying from 10 to 40 μ in length, with a posterior rod-shaped micronucleus, close to which is a very small basal granule or blepharoplast, from which the flagellum arises and passes forwards attached to the edge of a delicate undulating membrane and projects for a varying distance beyond the anterior end of the organism as a free flagellum, which drags the parasite forwards in swimming. The organism multiplies by division, first of the micronucleus and the flagellum, then of the centrally situated larger macronucleus, and finally the whole body divides longitudinally. With Leishman's method the nuclei and flagellum stain red, in contrast to the blue body. In fresh blood preparations, the living organisms are very active, and if numerous, as in Rhodesiense infections, may cause easily-recognised disturbances of the red corpuscles in the field of the microscope. They are often very scanty and hard to detect in the common Gambiense form of the disease. In both forms they are identical in appearance in the human subject, and they are more likely to be found during the occurrence of fever than in the afebrile intervals. They are more readily detected by centrifuging several cubic centi-

mide in blood ingested by tsetse-flies does not inhibit the development of the trypanosomes.

The difficult question is still debated whether *T. brucei* of cattle and antelopes is identical with *T. rhodesiense* of man, and whether the human disease can be transmitted from animals by tsetse-flies, but this view is losing ground. Thus, Corson failed to reconvert *T. rhodesiense* of man into *T. brucei* by transmission through antelopes, and it has been pointed out that in Zululand thousands of natives are bitten yearly by tsetse-flies infected with *T. brucei*, but sleeping sickness is unknown there. On the other hand, Corson has infected antelopes with *T. rhodesiense*, and H. L. Duke found that this parasite can maintain its cyclical transmissibility by glossina up to 600 days in an antelope, but he does not think these infected animals are as dangerous a menace to man as has hitherto been supposed. Corson has transmitted experimentally *T. rhodesiense* by *G. morsitans* from man to sheep and antelope and back again to man. The baboon, *Papio jubilæus*, has been experimentally infected by intrathecal inoculation.

Pigs have been found by van Hoof to be readily infected experimentally with *T. gambiense*; the infection can then be transmitted by tsetse-flies to man.

Tsetse-fly Destruction as a Prophylactic Measure. The elimination of tsetse-flies from the vast areas infected with sleeping sickness is very difficult but of the greatest practical importance in the control of trypanosome infections of man and cattle. In the small Portuguese island of Principe the disease was gradually brought under control by employing native boys to patrol the infected jungle at night and trap the flies on dark patches of cloth worn on their backs and smeared with birdlime. This plan was also successful in the Yaba area of the Southern Sudan in reducing the prevalence of sleeping sickness.

Clearing jungle along tsetse-fly infected streams is of more lasting value, if maintained yearly, especially against *G. palpalis* and *G. tachinoides*, which are closely confined to the borders of streams and are adversely affected by dry weather. Clearings are of most value around water-holes and at road and river crossings, where trypanosome infections are most likely to occur; but such limited clearings will not prevent the flies from spreading along the streams in the rainy season when the high humidity is favourable to their survival. In the Gold Coast more effective and lasting results were obtained by clearing trees and shrubs along the whole length of infected rivers, during each dry season, when the flies are most restricted in their distribution, and working downstream from the headwaters. Routine catches along the treated river during the wet season showed a reduction of the flies from 4,000 in an uncleared area compared with only 5 in a neighbouring cleared one, and the sleeping sickness hospital admissions fell by 90 per cent. In Nigeria a similar clearance together with 100 yard

1903 and later, Minchin, working with Sir David Bruce's Commission in Uganda, proved the occurrence of the same direct method of transmission to animals by the bites of infected *G. palpalis*. The flies ceased to transmit infection if they were kept two hours before being allowed to bite, as the parasites were quickly killed by drying. Minchin failed to find any cyclical development of the parasites in the insects or to cause infection by the bites of the flies at a later date.

In 1909 important progress was made when Kleine recorded experiments in East Africa with home-bred flies which were fed on monkeys infected with *T. gambiense*. By dissecting the flies which had fed, Kleine found that the trypanosomes, which disappear from the alimentary canal after a few days, again made their appearance in about 10 per cent. of the insects after twenty days. These positive flies were found to be infective to healthy animals after the reappearance of the parasites ; they were thus capable of conveying the disease twenty days after feeding on the infected animal, and remained so up to sixty-six or more days. These important observations were soon confirmed by Sir David Bruce and his colleagues, and the cycle of development has been traced to certain slender forms which reach the salivary glands, when the insects become infective and remain so during the several months of their existence. Repeated feeding of the flies appears to inhibit the development of the parasites, as in those starved after the first infective feed, as many as 21 per cent. may become infective to animals. The usual mode of infection is now believed to be through the bites of tsetse-flies in which cyclic development of the trypanosomes has taken place, but L. Duke holds that direct mechanical transmission was the common method under the special conditions of the great Uganda epidemic of sleeping sickness, when healthy and infected persons were closely aggregated in fishing boats. He also concluded that *T. gambiense* infections may at any time lose their power of being transmitted cyclically through *G. palpalis*, and that only some strains are capable of being spread by that method. Both *G. palpalis* and *G. morsitans* can be infected experimentally with the two forms of human trypanosomes, but in nature *G. palpalis* is the carrier of *T. gambiense* and *G. morsitans* of *T. rhodesiense*, In a summary of twenty-five years' experimental work on the still debated question on the infectivity for man of the brucei group of trypanosomes, *T. brucei*, *T. rhodesiense* and *T. gambiense*, H. L. Duke stated that no final conclusion regarding the original source of *T. rhodesiense* can yet be reached, but game probably plays only a negligible part in its spread. Nevertheless it is advisable to segregate man completely from game by sacrificing the game in settled areas. Success has been reported in South Rhodesia from controlled game-destruction and the creation of fly-free buffer zones. W. Yorke regarded all three organisms as varieties of the same parasite. Van Hoof found that the presence of a moderate amount of tryparsa-

two weeks in some Gambiense infections. In one instance the trypanosomes were found in the blood of a European in less than four weeks after arrival in the Congo area. A few laboratory infections

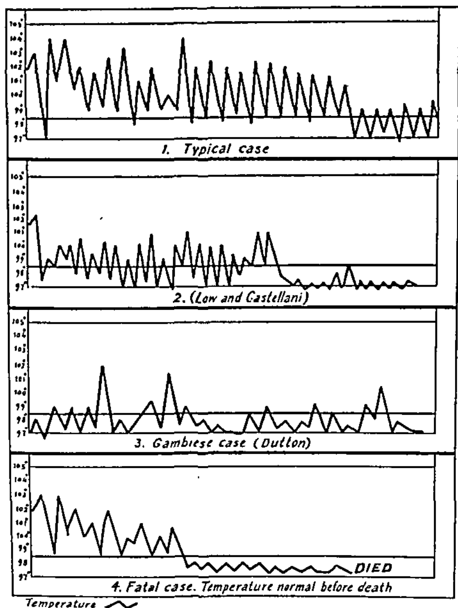


FIG. 16. Temperature charts of sleeping sickness.

also had similar short incubation periods. There is no evidence as to the maximum length of the incubation period.

Natural Immunity. A certain degree of resistance to infection has been attributed to the action of human serum on the causative parasites, but sensitiveness of a strain of trypanosomes to human serum does not preclude it from infecting man.

clearances on the boundaries have enabled important agricultural extensions to be made.

The destruction of large game as a preventive measure has for long been the subject of controversy. Twenty-five years' experience of the method in South Rhodesia in order to reduce the prevalence of *G. morsitans* had not established its value according to a committee report of 1945. In a severely infected area of Nigeria of 70 by 10 miles in extent limited waterside clearings have permitted 50,000 people with many cattle to live safely. In Kenya the importance of railways in carrying tsetse-flies was shown by the capture of many thousands outside the fly belts.

Pathology. The chief changes in the early stage are in the lymphatic system ; in the later sleeping-sickness stage the cerebrospinal system is also involved. The lymphatic glands of the neck and groin are usually enlarged, and after death those of the thorax and abdomen are also found to be affected ; microscopically, the glands show congestion and hæmorrhages, and, in long-standing cases, fibrosis may develop. We owe much of our knowledge of the lesions of the central nervous system to F. Mott, who found a round-celled infiltration of the perivascular lymphatic system, especially of the meninges, the brain and spinal cord. By the naked eye, congestion and a deposit of lymph may be seen in the meninges ; the lesions, as a whole, closely resemble those of general paralysis of the insane. Later, W. Yorke and others found that the trypanosomes invade the actual substance of the nervous tissues by escaping from the lymphatic channels. They are also present in the lymph glands, spleen, cornea and other tissues ; this accounts for the lesions and symptoms observed in the disease. In a child dying from a *T. rhodesiense* infection in Tanganyika, an enormous number of trypanosomes were found in ascitic fluid.

CLINICAL DESCRIPTION

Early Febrile Stage of Blood Infection. The early clinical stage of trypanosomiasis fever is related to the invasion of the blood stream and lymphatic glands by the trypanosome, while the later sleeping-sickness stage is caused by an invasion of the cerebrospinal system by the parasites. This distinction of the two stages is very important in connection with the prognosis and treatment, for the later stage is more refractory to treatment, and, therefore, more dangerous. Clinically, the early stage shows a picture which is quite different from the well-developed sleeping-sickness condition, but there is no sharp line of distinction between the two, and the onset of the more serious stage can only be detected at first by finding the trypanosomes or the richer cellular exudate and increased albumin in the cerebrospinal fluid.

The incubation period is said to be less than two weeks as a rule in the acute Rhodesian type of the disease, and it may be as short as

its size generally indicates some such complication as chronic malaria. The liver may also be enlarged. Weakness develops fairly early in the disease, and is progressive.

The earlier stages in which the trypanosomes have not yet invaded the cerebrospinal system may last for months or years in the milder types of the disease. During this period there may be considerable intervals of freedom from fever and other symptoms ; in rare cases the disease may apparently cease to progress, and recovery may take place, especially if efficient treatment is carried out. In the vast majority of untreated or inadequately treated cases, the disease gradually passes into the more serious and intractable sleeping-sickness stage, during which the trypanosomes may be found in the cerebrospinal fluid drawn off by lumbar puncture. There is also a great increase in the leucocytes and albumen of the cerebrospinal fluid, and the earliest indication of involvement of the nervous system may be obtained by such examinations. The symptoms met with in the later stages are as follows :—

Sleeping-Sickness Stage with Cerebrospinal Involvement. Nerve Symptoms. In this more advanced condition nervous symptoms naturally predominate : these include headaches of increasing severity and frequency, fine tremors of the tongue, occasionally also of the hands, together with pains and cramps. Kerandel's sign of severe deep hyperæsthesia of the muscles on pressure, or following a slight blow, is usually present, and may be a fairly early symptom. Other alterations in sensibility, combined with weakness or paralysis of muscles, develop, and convulsions occur at times. The whole picture rather resembles that of general paralysis of the insane, but the Argyll-Robertson sign of loss of the reaction of the pupil to light is not seen. Asthenia now increases, and the patient loses all energy and lies in a somnolent condition, although he can be easily roused, except in a very late stage of the disease. The expression now becomes vacant, and the mental condition is one of dulness or melancholia. Other psychical troubles may appear, and eventually the patient becomes comatose and dies in this condition. Death may occur after a period of advancing general weakness, or may result from some complicating disease, such as pneumonia or dysentery.

Complications. Eye symptoms due to invasion by the parasite occur in the form of keratitis, iridocyclitis and choroido-retinitis in the terminal stages of sleeping sickness associated with secondary infections of the meninges and the central nervous system. In cases treated by arsenical preparations, optic atrophy, sometimes followed by blindness, may result from the large doses of the drugs which are required. Visual disturbances occurred during treatment in 20 per cent. of second-stage cases under the care of F. van den Branden and M. Appelmans, but they may less frequently occur in untreated cases and so are due to a combination of toxins and arsenical preparations,

Primary Lesion. A primary lesion at the site of the bite of an infected tsetse-fly may occasionally occur in the form of an indurated button-like reddish swelling up to 10 cm. in diameter. In acute infections trypanosomes may appear in the blood after seven to ten days and puncture of glands may also show the organisms and establish the diagnosis.

The onset may be sudden with high fever, or insidious with only occasional irregular rises of temperature with no definite characteristics. The early symptoms are fever at irregular intervals, general enlargement of the superficial glands, especially those of the lower part of the neck. In the milder types, seen mostly in West Africa, the patient presents little sign of illness, and the occasional attacks of fever are very likely to be mistaken for malaria. The early more amenable stage is very likely to be overlooked unless the physician is constantly on the look out for the disease in the affected areas (*see* Fig. 16, Charts 1 to 4).

The pulse is rapid—it varies from 100 to 140 during the fever and may continue to be rapid even when the temperature is normal; its tension is low. Myocardial sclerosis has been observed in fatal cases.

An erythematous rash is frequently seen in the early febrile stage in Europeans. It has an annular or blotchy appearance, is ephemeral in nature and is most evident on the chest and back, but may also occur on the extremities and face. A mottled blue discoloration of the skin of the abdomen is of frequent occurrence. In the dark-skinned natives of Africa rashes are very difficult or impossible to detect. Papular or vesiculo-papular eruptions and a rash resembling erythema nodosum have also been recorded. Localised œdema of the face or the feet is of frequent occurrence.

Enlargement of the lymphatic glands is a still more important early symptom of the disease, especially from the diagnostic point of view. Any of the superficial glands may be involved, but the most characteristic glandular enlargement occurs in the anterior and posterior triangles of the neck in the form of separate rather soft prominence of the glands, which may have the consistence of plums, but in chronic cases they may become harder from fibrosis. Arab slave-dealers, more than a century ago, were well aware that sleeping sickness was likely to develop in negroes who had enlargement of the glands of this kind. The significance of the glands is greatly enhanced now that it is known that the causative trypanosomes can be found readily in the fluid obtained by gland puncture, even when no organisms can be found in the peripheral blood stream. The glands may reach the size of a pigeon's egg, and when the enlargement is great from 80 to 90 per cent. of them will be positive to trypanosomes on puncture, a proportion that decreases with the size of the glands until those just palpable may only show about 5 per cent. of infections.

The spleen may be moderately enlarged, but any great increase in

gives a negative result, several cubic centimetres of blood should be mixed with a little sodium citrate solution to prevent clotting, and centrifuged for several minutes ; the supernatant fluid is removed and is centrifuged a second and a third time, when any parasites will be found in the deposit. A still more delicate test is to inoculate some of the patient's blood into a rat or guinea-pig, for if either of these animals becomes infected the trypanosomes multiply exceedingly in the blood, and can be detected easily in a fresh specimen by their movements. The blood becomes positive after a week or more, so that this method involves delay. Corson, in all but one of several volunteers, observed that on inoculation with trypanosomes the appearance of local swelling at the site of injection associated with axillary pain, usually after five to seven days was a sure sign of infection.

Puncture of enlarged lymph glands is a more reliable and rapid method of diagnosis ; the glands of the posterior triangle of the neck are the most convenient for the purpose. In the fluid drawn off the trypanosomes are readily found in either fresh or stained specimens. A. Broden, in the Belgian Congo, obtained positive results in 87·7 per cent. by gland puncture, and in 80·7 per cent. by triple centrifugation of 10 c.c. of blood with 1 c.c. of 6 per cent. citrate solution, but by lumbar puncture they were only obtained in 4·5 per cent. Trypanosomes may also be found in many cases in bone marrow obtained by puncturing the sternum.

In the later stages of sleeping sickness examination of the cerebrospinal fluid removed by **lumbar puncture** is a valuable method to detect the involvement of the meninges at an early period. Trypanosomes may be found in the fluid, and if they are too few to be detected, even by centrifuging the fluid, the estimation of the amount of albumen, which is normally 0·10 to 0·15 per thousand, will give valuable information. So also will a leucocyte count, as the normal number is only one to three per cubic millimetre, while in sleeping sickness the *leucocytes in the cerebrospinal fluid may reach 1,000 to 2,000* per cubic millimetre. Lefrou and Ouzilleau, in the Congo area, believed that albumen over 0·20 per mille, and a cell content of over 50 per cubic millimetre indicated a meningeal reaction of diagnostic value, and showed the onset of the second stage affecting the central nervous system. The number of cases showing trypanosomes in the cerebrospinal fluid increases in proportion to the height of the leucocyte count.

The serum-aldehyde test (*see* p. 75), gives well-marked reactions in many cases of trypanosomiasis. The reaction decreases or disappears with recovery under tryparsamide treatment.

Prognosis. In the milder Gambiense form this is now good with the present treatment if the disease is recognised in the early stages, and even after the second sleeping-sickness stage has developed there is very fair hope of recovery under tryparsamide, except in very late

of which tryparsamide is less dangerous than atoxyl. They are more frequent in proportion to the degree of pathological changes in the cerebrospinal fluid and the consequent involvement of the nervous system. Contraction of the field of vision is an early symptom, but recovery takes place if arsenicals are at once discontinued. Abortion has been found to be frequent in sleeping-sickness cases in the Congo area.

The blood may show anæmia, which is slight in the early stages, but is likely to be severe towards the end ; there are no constant changes in the leucocyte count but there may be an increased proportion of large and small mononuclears. Auto-agglutination of the red corpuscles is frequently seen in fresh specimens of the blood.

The cerebrospinal fluid in the sleeping-sickness stage may be slightly turbid and contain an excess of albumen ; by centrifugation, an excess of lymphocytes and large mononuclear leucocytes may be found. Trypanosomes are also often found ; both of these findings are of diagnostic and prognostic importance, as they indicate invasion of the meninges by the parasites.

The duration of the disease is extremely variable. So long as the infection remains limited to the blood, and to the lymph streams other than those of the cerebrospinal system, the common Gambiense form may run a very protracted course of several years, while the more virulent but rarer Rhodesiense form runs a rapid course which is usually measured in months. In either variety it is found that when symptoms of invasion of the nervous system have set in, the usual duration is from four to eight months in untreated cases. The disease in this stage used to be invariably fatal before the discovery of tryparsamide.

DIAGNOSIS

This is very difficult in the early stages, but very easy in advanced cases seen in endemic areas or during the prevalence of an epidemic. It is of paramount importance to recognise the early febrile stage while the infection is limited to the blood, because this period of the disease is far more amenable to treatment, so it requires separate discussion.

In the early stages the diagnosis depends on finding the causative trypanosome in the peripheral blood or in the enlarged lymph glands. Examination for the parasites should be carried out in every obscure case of fever in the endemic areas ; but malaria should first be excluded (*see* p. 32). The occurrence of enlarged glands, especially in the neck, or the appearance of the erythematous rash in fair-skinned persons, should lead to a suspicion of trypanosamiasis. The trypanosomes are most easily detected by their movement in a drop of fresh blood or gland fluid under a coverslip. They also stain well by Leishman stain, but are usually scanty except in the Rhodesian type, and so may be found only after a very prolonged search. If such a simple examination

place in the condition of the cerebrospinal fluid with arrest of the symptoms in the second stage of the disease. Thus in the Belgian Congo 75 per cent. of 11,000 cases followed up for two to ten years were cured, and under favourable conditions 80-90 per cent. may be cured with great reduction in the incidence and mortality of the disease. Dimness of vision is liable to occur with the larger doses more especially, but if careful watch is kept for the first symptoms they clear up in the great majority of the cases on the drug being discontinued. Toxic effects are reduced by using distilled rather than boiled water for dissolving the drug.

Diamidines. Yorke and his colleagues in Liverpool found that certain aromatic diamidines are effective against human trypanosome infections of small animals ; they have also proved active in the human disease. The most generally used is **pentamidine** (4 : 4-diamidine diphenoxy pentane) in doses of 3 mg. per kilo of body-weight, intramuscularly or intravenously, on alternate days or daily for five to ten doses. This treatment is effective only in first stage cases before cerebrospinal involvement. It should not be given intrathecally on account of its toxicity by that route. A single dose of 2 mg. per kilo of body-weight intravenously is reported to have a prophylactic action lasting for at least six months. It may be effective in early cases that have become resistant to other drugs. Diamidines have also proved to be of great value in early cases treated in French West Africa.

Melarsen Oxide has been recommended by Friedheim as being more effective than tryparsamide in the late cerebrospinal stages of the disease. In the Belgian Congo good results have been reported in 80 per cent. of second-stage cases resistant to tryparsamide. A new form " Mel B " is said to be less toxic and to be of value in all stages of trypanosomiasis ; it is given in two series of four intravenous injections of 3·6 mg. per kilo with an interval of one week between the two series. Further trials are indicated.

Mass Treatment in the Control of Sleeping Sickness. In Nigeria an increase of sleeping sickness was attributed to greater infection following increases of agriculture. It was dealt with successfully by mass treatment with suramin of all the cases discovered by surveys of three million people at rural health dispensaries. An original incidence of 20·5 per cent. was thus reduced to 2·1 per cent. In the gold-fields where compulsory examinations were carried out every six months treatment reduced the incidence from 35 to 0·4 per cent. and the disease is now under control. Similar methods have been successful in the Belgian Congo. The outlook for the control and great reduction of the incidence of trypanosomiasis in Africa has been greatly improved by recent advances in treatment and by the prophylactic use of the drugs now available.

A case has been recorded in which the organism disappeared from the blood after the administration of penicillin.

cases. In the more virulent *T. rhodesiense* infections the prognosis is more grave, but recoveries are not infrequent. The number of cells in the cerebrospinal fluid is of little significance in prognosis, but the higher the percentage of albumen the worse the outlook. H. Fairburn (1934) also found that a low percentage of protein in the cerebrospinal fluid indicated an intact nervous system and prospect of a ready cure by Bayer 205, but in early cases resistant to this drug the protein is high, even within a month of onset.

TREATMENT

Historical. At the time of the discovery of the causative trypanosome the only drugs known to have a limited action in the early stages before the cerebrospinal system became seriously involved *were the arsenical preparations, sodium antimonyl tartrate, atoxyl* and soamin. Thanks to chemotherapy the more effective remedies described below have now been discovered.

Suramin (Bayer 205, antrypol or moranyl). In 1920 this drug was found rapidly to free the blood of infected animals of trypanosomes. It also proved active in destroying the organisms in the blood and lymph glands but was of much less value in the later sleeping-sickness stages with involvement of the cerebrospinal system ; but it has the advantage of seldom causing the serious eye complications that may follow the use of some arsenical preparations.

The **Dose** is 1 gm. in 10 c.c. water intravenously weekly for five weeks up to a total of 5 gm. The first dose may be only 0·5 gm. Watch must be kept for renal irritation with albuminuria and for toxic dermatitis, which are indications for stopping the treatment for a time, when they readily clear up. If this treatment is carried out within a month or so of the onset of the first symptoms recovery is the rule, but relapses are not infrequent.

Prophylactic Value of Suramin. For this purpose the dose is 1·5 gm. in adult males, 1·25 gm. in females and 0·03 gm. per kilo body-weight in children, given intravenously and repeated after three months. Persons visiting endemic areas of the disease for limited periods can thus be protected against infection. A Belgian focus of infection among 1,500 persons was eradicated by two injections given at an interval of three months, *although cases continued to occur in* an untreated control area.

Tryparsamide is an arsenical preparation (sodium *n*-Phenyl-glycineamide-*p*-arsonate) which is much more effective than suramin in the later sleeping-sickness stage of the disease. It can be injected intravenously or into muscles in a 10 per cent. solution in weekly doses of 3–5 gm. in adults and 0·5–2 gm. in children up to a total of 20–50 gm in adults. Trypanosomes disappear from the blood in a few hours and remain absent for several weeks. *Improvement takes*

in the blood. Keratitis and conjunctivitis are frequent complications, and the child commonly dies in twenty to thirty days. The disease was *first found in an area where endemic goitre is prevalent, and was* described as parasitic thyroiditis. Later, Kraus and others found it in areas of Argentina and Panama in the absence of goitre, which is not now thought to be an essential feature of the disease.

The cardiac changes are the most characteristic feature; large nests of parasites are found in or between the muscular fibres of the heart in acute cases with extensive infiltration of leucocytes. This results in a diffuse myocarditis which is the most constant lesion in children dying in the acute stage of the disease. In chronic cases fibrotic changes with myocardial degeneration ensue.

"Inoculation Chagomata" (local tumours at the sites of bites by infected bugs) have been described by Vazza; metastatic growths may occur later in other parts of the skin. The tumours develop within a few days, and vary in size from small papules up to the size of an orange. Leishmania forms of *T. cruzi* have been found in sections of the nodules, which are reported to improve rapidly on 90–120 mg. per kilo of Bayer 7602.

The chronic form *ensues in those who survive the acute febrile* stage. It is characterised by widespread œdema, usually beginning in the face, which may be hard, not pitting on pressure, cardiac irregularity sometimes ending in failure of the heart with tachycardia or bradycardia, extra systoles, auricular fibrillation, arrhythmia and syncope. Suprarenal deficiency with the symptoms of Addison's disease, or nervous symptoms with motor paralyses, choreic movements and sensory and mental disturbances may develop according to the main location of the visceral infection. There is, however, some difference of opinion regarding the range of symptoms attributable to this infection.

Diagnosis. In the acute stage this may be made by finding the trypanosomes in the peripheral blood either directly or after centrifuging it in citrated saline. If microscopical examinations fail it is necessary to inoculate guinea-pigs or puppies with the blood of the patients, and subsequently to examine their internal organs for the tissue stage of the organism, but even this plan fails in chronic cases, when one of the following tests may be of use.

Xenodiagnosis of Brumpt (1914) consists of feeding clean carrier bugs on the patient, and ascertaining if they become infected with the parasite, which has occasionally proved to be the case.

The Machado reaction is a complement deviation test in which the antigen consists of a glycerine and watery extract of the heart or spleen of infected animals, such as puppies. It is quite independent of the Wassermann reaction, as antigens made from normal animals do not give positive results and uniformly negative ones were obtained with persons uninfected with Chagas's disease. Several observers have claimed 80–90 per cent. of correct results with this test, and Ev.

SOUTH AMERICAN TRYPANOSOMIASIS OR CHAGAS'S DISEASE

Definition. This is a form of human trypanosomiasis met with in South America caused by *Trypanosoma cruzi* and disseminated by various reduviid bugs ; it is characterised by an acute febrile stage with involvement of the lymphatic glands, spleen, and nervous system ; and a chronic stage with invasion of the heart muscle by the parasite.

It is widespread in Brazil, and also prevalent in other parts of South America, such as Venezuela, Peru, Uruguay and Argentina and also in the Central American areas of Panama and Salvador. From a survey of the literature W. Yorke (1937) found that most cases have been met with in the Brazil State of Minas Geraes where C. Chagas first discovered it, together with a few in Saõ Paulo. Outside Brazil he only found records of 113 cases, including eighty-three in Argentina ; although the carrier bug is very widely distributed in Central and South America.

Ætiology. In 1909, the causative trypanosome was discovered in children in Brazil by Cruz and Chagas, who showed that the organism developed in the intestinal canal of the bug *Triatoma megista*, which can transmit the disease under experimental conditions to man and domestic animals, probably through the infected fæces coming into contact with the bite of the insect, and not through the bites of the bugs as was at first thought. Infection through the conjunctiva has been reported ; the buccal, vaginal and rectal mucosæ are also held by some to be channels of infection. The trypanosome undergoes a complicated development in the insect, of about ten days' duration, and it can be cultivated on N.N.N. medium. Such South American animals as the armadillo and the opossum are believed to act as reservoirs of infection. The larval, nymphal and adult stages of the bug may all become infected with the trypanosomes from the blood of human patients ; these insects are abundant in the houses of the poor. The parasite has been found in the blood of blood donors, who may remain infected for many years without showing active symptoms. Carriers of infection can be detected by complement-fixation tests.

Pathology. The main peculiarity of the American form of trypanosomiasis, which has led some to class the parasite as a *Schizotrypanum*, is that, in addition to the flagellate stage found in the peripheral blood, a leishmania non-flagellate form is found in masses in the internal organs, especially in the heart muscles, and also in the nervous system, the thyroid, suprarenals, ovaries and testes. In dogs infected with the disease the damage to the cardiac muscles has been found to be due to the mechanical pressure of the rapidly multiplying parasites.

Clinical. In the acute form, most frequently seen in young children, fever occurs early and continues as long as the trypanosomes are found

CHAPTER IV

THE RELAPSING FEVERS AND RAT-BITE FEVER

THE RELAPSING FEVERS

Definition. Two distinct diseases are called relapsing fever; these resemble each other: (1) in being caused by nearly related spirochætes; (2) in being transmitted to man by arthropod vectors; and (3) in showing the same general type of clinical symptoms. They, therefore, belong to the same group. They differ from each other in that one is transmitted from man to man by human lice and so can suitably be called louse-borne relapsing fever or louse relapsing fever; the other is transmitted to man by ticks, often from lower animals, and is best called tick-borne relapsing fever or tick relapsing fever. They should be called the relapsing fevers rather than relapsing fever.

The chief points of difference between the two kinds of relapsing fevers are shown in the following table:—

THE RELAPSING FEVERS

	Louse relapsing fever.	Tick relapsing fever.
Cause . . .	*Spirochæta (Borrelia) recurrentis.*	*Spirochæta (Borrelia) duttoni.*
Vectors . . .	Human lice.	Various ticks.
Transmission . .	Man to man.	Lower animal to man or man to man.
Epidemiology . .	Tends to be epidemic, and is cosmopolitan.	Sporadic or in small outbreaks, confined to certain localities.
Usual number and duration of spells of fever.	One to three spells, each lasting three to ten days.	Four or more spells, each lasting one to four days.
Periodicity of the fever	Of the 12- to 16-day type in most cases.	Variable but shorter in most cases.
Number of spirochætes in the blood during the febrile spells.	Numerous.	Few or very few.

LOUSE RELAPSING FEVER

Definition. A fever with a pronounced tendency to the occurrence of one or more relapses caused by a spirochæte (*Spirochæta recurrentis* or *Borrelia recurrentis*), which is transmitted from man to man by human lice.

History. Cases were described by Hippocrates 2,000 years ago in Thrace.

In 1770 Rutty of Dublin described it as "Five or Seven Days' Fever with Relapses."

In 1843 Henderson of Edinburgh showed that it was quite different from typhus fever with which it had previously been confused.

Chagas (1934) obtained positive results from the tenth day onwards in cancer patients who had volunteered to be infected artificially with this disease.

Treatment. Unfortunately the antimony and arsenic preparations that are of value in African trypanosomiasis have failed in the American variety. Several observers, however, have recently reported good results from treatment with the preparation known as Bayer 7602, the composition of which does not yet appear to have been disclosed by the German makers.

Prophylaxis. The large black-bug carrier lives in crevices of the grass walls and roofs of the houses of the poor on whom it feeds at night, so cleanliness, fumigation, and the use of mosquito curtains at night are promising modes of prophylaxis. The possible animal reservoirs of the parasite should also be avoided. Treatment of the huts by DDT or gammexane is of value.

LEONARD ROGERS

In 1876–77 Vandyke Carter, in Bombay, found the spirochaete in Indian patients ; he conveyed the disease to monkeys and men by injecting infected blood.

In 1907 F. P. Mackie, in India, incriminated the body louse as the important vector.

In 1907–8 Ed. Sergent and Foley demonstrated the transmission of the disease by lice.

Geographical Distribution. Like louse-borne typhus fever, the disease tends to occur in epidemic form over wide areas, and to die down for several years, remaining in small foci from which it spreads when conditions become favourable. The disease cannot exist in the absence of lice, and is now very rare in cleanly civilised communities. It was once common in Great Britain and other European countries

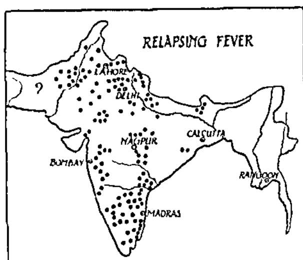


Fig. 18. Map of distribution of relapsing fever in India in 1917–24.

which are now free from the disease. Great epidemics occurred in Eastern Europe during and after the 1914–18 War, and again in 1942–45 thousands of cases occurred in Egypt and North Africa. Australia and the others countries included under the name Australasia are the only parts of the world from which the disease has never been reported.

The countries in which epidemics have occurred in recent times are : Eastern Europe, Northern Asia, India, China, Western Asia, North, South and Equatorial Africa.

Lesser outbreaks have occurred in Peru, Central America, French Indo-China and Japan.

In the Punjab, and probably in other parts of India, epidemics occurred in 1869, 1878, 1891, 1906 and 1920. In the last epidemic the disease first appeared in certain parts of the country and gradually increased in severity and extent ; it was first detected in the United Provinces in 1912, and by 1917 became a severe epidemic in that part of India. By 1920 it had become widespread over the greater part

STORY OF AN ATTACK OF LOUSE RELAPSING FEVER

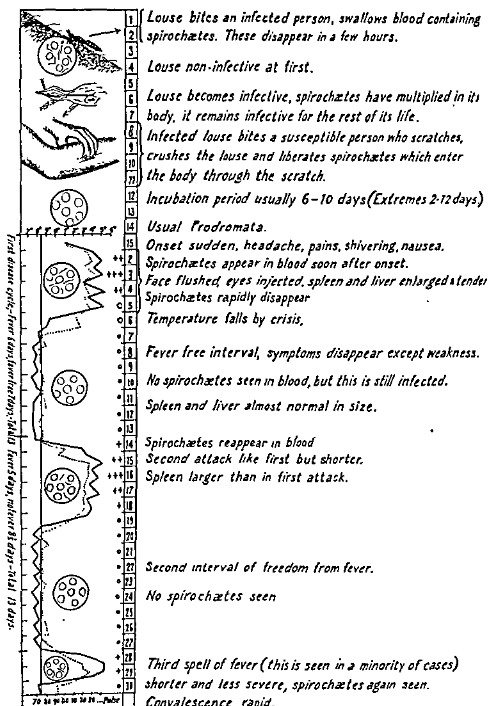


FIG. 17. Story of an attack of louse relapsing fever.

In 1852 Lyall recognised the disease in the Punjab.
In 1868 Obermeier, in Berlin, discovered the spirochætes.
In 1874 Münch, of Odessa, conveyed the disease to himself by inoculation with the blood of an infected person.

possible but this cannot be an important mode of transmission. The sequence of events is shown in Fig. 17.

Immunity. This is complete for a variable period of time after

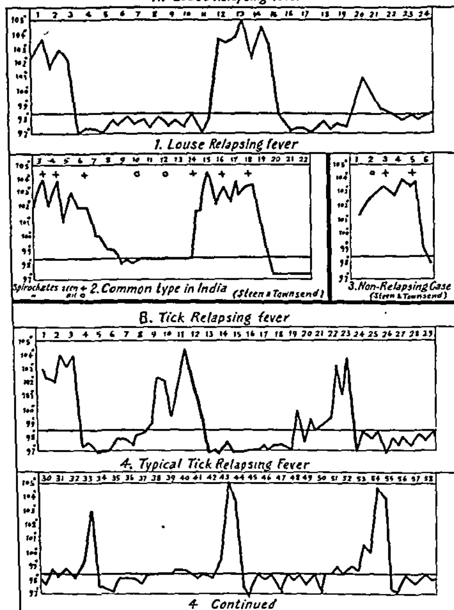


FIG. 19. Temperature charts of relapsing fever.

an attack. In a few cases second attacks have occurred within a few months. After widespread epidemics the whole community acquires a sufficient degree of mass immunity to prevent the occurrence of further epidemics for several years.

Pathology. There are no characteristic changes in the body after

of India. From 1924 the disease gradually subsided, so that since 1929 it has persisted only in scattered foci. Further epidemics are likely to occur at intervals in India.

Seasonal Distribution. Louse infestation and overcrowding are greatest during cold weather so that in north latitudes the disease increases in prevalence during the winter and the peak of incidence is usually in early spring ; it tends to die out in summer when conditions are not favourable for transmission by lice. In countries in which the weather is cool all the year round epidemics may occur at any season of the year.

Age, etc. The disease is more common in adults than in children, probably because the soft, feeble fingers of a child cannot crush the lice.

Louse relapsing fever, like louse typhus, attacks communities which are louse-infested, crowded and poverty-stricken, therefore it is specially common in times of famine and war. It often occurs simultaneously with, or after, epidemics of typhus fever, though for some unknown reason India has not suffered heavily from louse-borne typhus in spite of the conditions being apparently favourable to its occurrence.

The Spirochæte. This is named *Spirochœta* (*Borrelia*) *recurrentis.* It is a long spirochæte (usually 10 μ to 20 μ in length) and is extremely slender (0·32 μ) ; it has three to six turns and is pointed at both ends. It stains well with Leishman's stain and with most of the ordinary dyes, and is Gram-negative. In moist blood preparations it is actively motile and tends to form clumps. A peculiar feature is its tendency to disappear suddenly from the blood twenty-four to thirty-six hours before the fall of the temperature. During the afebrile stage the blood is still infective to animals, though spirochætes can rarely be detected in blood films taken while the temperature is normal. The spirochæte passes, though not readily, through Berkefeld candles ; it can be cultivated in Noguchi's medium and in chick embryos. It is readily inoculable to monkeys, but with difficulty to other adult animals except after a preliminary passage through monkeys or through newly-born mice, rats or rabbits which have recently been found susceptible.

Transmission of Infection. When a louse has fed on an infected person it swallows the spirochætes with its blood meal ; very soon the spirochætes can no longer be found in the stomach contents of the louse, but about five to ten days later the organisms can be found in the body fluids of every part of the insect. When the louse finds a new host in the course of its wanderings and bites him he is likely to scratch to relieve the irritation and in doing so he crushes the insect and so discharges its infected body fluids from which the spirochætes enter the skin through abrasions caused by scratching. Direct infection by contact with the infected blood of a patient is believed to be

Spleen and Liver. These are enlarged in many cases and are often tender; the enlargement may be considerable, it becomes less during the fever-free periods, and increases again when the fever returns.

Jaundice occurs in 20–60 per cent. of the cases during one or other spell of fever; when slight it is of little importance.

Respiratory System. Bronchitis with hurried breathing and cough occurs in 40–80 per cent. of cases; there is scanty sputum with the cough.

Epistaxis is common in some outbreaks; it occurs in 5–30 per cent. of the cases.

Cardio-Vascular System. The pulse may have no characteristic feature, but sometimes is slow relatively to the height of the temperature. The apex beat of the heart may be displaced outwards and there is a distinct tendency to heart failure during and after the attack.

Blood Changes. Spirochætes can usually be found at the onset of each spell of fever; they increase in number till the fever reaches its highest point. A day or two before the temperature falls to normal they rapidly disappear. They can seldom be found during the afebrile periods even in thick films, though the blood is still infective at this stage.

There is usually a moderate degree of leucocytosis.

Urine. Albumen and granular or hyaline casts occur in severe attacks. Spirochætes can often be found in the centrifuged deposit.

Rash. In white skins a diffuse erythema is sometimes seen on the back of the neck and shoulders, spreading to the chest, back and arms. It is seldom visible on pigmented skins.

Eyes. Iridocyclitis occasionally occurs; recovery is usually complete. Photophobia and conjunctival injection frequently occur.

Nerves. Neuritis of the facial nerve occasionally causes facial paralysis which in rare cases may be permanent.

Diagnosis

When the disease is suspected and spirochætes are looked for, diagnosis is usually easy and certain, but spirochætes are often missed when blood films are examined in a routine manner without making a special search for the parasites; although they are unmistakable when seen, they are so slender that the eye can easily overlook their presence. It must be remembered that the spirochætes are scanty at the beginning of each fever spell, and that they disappear quite suddenly towards the end of the fever. A single negative result does not justify the exclusion of relapsing fever, even when the blood is taken while the temperature is high. Films prepared and stained in the same way as for malaria parasites are quite satisfactory.

In cases with a relapse the temperature chart is highly characteristic, but sometimes the first case in an outbreak has only one spell of fever so that suspicion is not aroused till valuable time has been lost.

death. The spleen is usually large and soft; there may be jaundice and petechiæ. Spirochætes cannot be found in the blood after death.

Clinical Features

Incubation Period. This is usually five to eight days; it may be as short as two days or as long as twelve.

The Onset: This is sudden or rapid, sometimes with rigor; headache and body pains are usual; there may be sweating, nausea or vomiting; epistaxis is not uncommon in some epidemics.

Features of the Attack. In the early stages there is seldom any feature by which the disease can be distinguished from other acute fevers except the presence of spirochætes in the blood, and these will seldom be detected unless they are specially looked for. The temperature rises rapidly, reaching 102°–104° F. within twelve to twenty-four hours. Continued or remittent fever lasts for three to ten days (usually six to eight) and ends by crisis or rapid lysis followed by a period of subnormal temperature lasting twelve to twenty-four hours as a rule, and often accompanied with sweating and a tendency to collapse in severe attacks. In 10–50 per cent. of the cases in different outbreaks there is no further rise of temperature, but usually a relapse occurs on the twelfth to the sixteenth day after the onset; this tends to be shorter and less severe than the first spell of fever, otherwise it is similar. A second relapse may occur, or even a third or fourth; the onset of each relapse tends to occur at an interval of twelve to sixteen days after the onset of the previous spell of fever irrespective of the duration of that spell, so that there is a tendency to a uniform periodicity in the occurrence of the relapses, each period being made up of the duration of the spell of fever added to the duration of the fever-free interval which follows. For example, when the periodicity is of the fourteen-day type the fever spell may last nine days and the afebrile stage five days or the fever may last five days and the afebrile stage nine days. Irregularities often occur, but in the relapsing fevers and in other fevers with recurrences the periodicity is often helpful in diagnosis.

The number of relapses in different epidemics is very variable: in 10–50 per cent. there is no relapse; in 25–65 per cent. there is one relapse; in 10–40 per cent. there are two; in only about 1–2 per cent. there are three; very rarely there are four.

Other Features

Pains. Severe pains in the back and limbs are usual, they may be specially severe in the shins.

Alimentary System. Nausea or vomiting occurs in 30–60 per cent. of the cases; there is loss of appetite, the tongue is dry and coated, and may be covered with sordes in severe cases. Constipation is usual.

use of aureomycin in tick relapsing fever suggest that this drug and chloromycetin can be expected to be curative.

Penicillin in very large doses has been advocated by some medical men.

Prevention

The disease can be prevented in the way found so effective for louse typhus by the application of a dusting powder containing 5–10 per cent. of D.D.T. to the body, clothing and bedding of patients and of everyone who has been exposed to risk of infection. A second application should be made a week or so later. Arrangements should be made for dusting the whole community at special centres at which the staff employ dusting guns provided with nozzles so that the dust can be applied by inserting the nozzle at suitable places without removing the clothing. The powder must reach the whole surface of the body and hair and must also be applied between the layers of the clothing ; it should not be brushed off or washed away because it is important to preserve its residual effect on larvæ hatched out from the eggs on which D.D.T. has no lethal effect. Apart from persons already infected the effective dusting of the whole community will quickly bring an epidemic under control. If practicable it is better to disinfest the occupants of every house with their bedding and clothing at their homes and to repeat the process every week till cases cease to occur.

For persons already attacked the first step should be to dust them before sending them to an isolation hospital where they will be bathed, shaved and provided with clean clothing impregnated with D.D.T. before being admitted to the ward. Their own clothes will be disinfected by heat before being stored.

If a suitable dusting gun is not available the next best plan is to apply the dust by hand, but this necessitates the removal of the clothing so that the staff cannot deal with so large a number of persons.

Every person engaged in preventive work or attendance on the sick should wear louse-proof clothing impregnated with D.D.T. by dipping it in a wettable emulsion of the substance and then drying it. The workers should be young and healthy.

The people of some tropical countries have the useful habit of rubbing a little vegetable oil into the skin and hair after bathing, this practice discourages infestation with lice, and it would be still more effective if D.D.T. were added to the oil to make a solution of about 1 per cent.

TICK RELAPSING FEVER

Definition. Tick relapsing fever is caused by *Spirochæta* (*Borrelia*) *duttoni*, which is transmitted from lower animals to man or from man to man by various species of *Ornithodorus* ticks.

In view of the great importance of early recognition of the disease, an attitude of watchful suspicion must be adopted. Dengue, malaria and typhus fever are the diseases most likely to give rise to errors in diagnosis, but if modern methods of examination are employed there should rarely be any difficulty in making the diagnosis. A positive Weil-Felix reaction with *Proteus OXK* has been described by several observers as occurring in the great majority of their cases.

Prognosis

The mortality in different epidemics varies from 1 to 50 per cent., the average being about 10 per cent. Epidemics are more fatal in times of famine. As a rule the spirochætes are more numerous in severe than in mild attacks. The prospects of recovery depend on the severity of the attack, the treatment that is given, the previous state of health, and the age of the patient. Few deaths occur in patients under thirty years old unless they have been debilitated by starvation or previous illness. The risk to life is great after the age of fifty, and after sixty few patients recover in severe outbreaks.

Treatment

Complete rest is essential during the attack and in convalescence. The special danger is heart failure ; this is most likely to occur at the time of the crisis, so that the patient needs special care when the temperature is falling and just afterwards. Plenty of water should be given, the diet should be liquid ; it is not necessary to force food on the patient during the first day or two of each paroxysm, but he must be encouraged to take a nutritious diet as soon as the temperature falls. The diet should be rich in vitamins, especially vitamin C. The drug treatment has hitherto been by novarsenobillon or neoarsphenamin given very slowly in a single dose of 0·6 gm. intravenously.

The drug should not be given if there is evidence of organic disease of the cardio-vascular, renal or hepatic system ; it should never be given just before the crisis is expected nor during the crisis, because serious collapse may follow. The time to give the drug is soon after the onset of the spell of fever or at the height of the paroxysm while spirochætes are still numerous in the blood stream ; in most cases the paroxysm will be cut short. Relapse occurs in less than 15 per cent. of the cases treated in this way.

The weight and general condition of the patient must be taken into account ; 10 mg. for each kg. of weight is considered suitable as a maximum dose, but if the patient is in a debilitated condition the dose should be reduced by one-third. It is often a matter for anxious consideration whether the patient's chances of recovery are greater with or without the drug.

The good results reported by Gilchrist and Yeo (1950) from the

tality rate tends to be lower than that of louse relapsing fever, but in some places it is high.

(6) The fever spells are more intense but are of shorter duration, seldom lasting more than two to four days. The periodicity of the fever tends to be irregular and is seldom of the twelve- to sixteen-day type commonly seen in louse relapsing fever. Expected spells are sometimes missed out and there are often small spikes of fever between the main spells. The number of spells is greater ; usually five or more (see Fig. 19).

(7) Neuritic manifestations are more common ; meningitis, hemiplegia, facial paralysis and neuritis affecting other cranial nerves are relatively frequent.

(8) There is usually a greater resistance to arsenical treatment ; indeed, many medical man are doubtful of its value.

Prevention. Avoidance of tick-infested houses and camping grounds or the destruction of the ticks by dusting their haunts with D.D.T. or " Gammexane " are helpful. The ticks bite chiefly by night so that mosquito nets are useful.

Tidy rat-proof houses with cement floors and smooth walls are unlikely to be infested with ticks.

Ticks in the burrows of rats and other animals are often infected, so that the bites of ticks in the open country must be avoided. When a tick attaches itself a drop of kerosene or turpentine should be applied ; if in spite of this it does not drop off or cannot be removed by gentle traction, a small wedge of skin including the mouth parts should be snipped off with a pair of scissors. A drop of pure carbolic acid should be applied to the site of the bite.

Diagnosis. This is best made by finding the spirochætes, but these may be very scanty even at the height of the fever. The temperature chart is usually characteristic.

Treatment. This is the same as for louse-borne relapsing fever except that the arsenical injections are given three or four times at intervals of 5–7 days ; they often fail. Streptomycin injections in doses of 0·5 gm. twice daily for two days have been recommended.

Aureomycin has been found effective ; this or chloromycetin (chloramphenicol) in doses of 0·5 gm. can be given every six hours for six or eight doses, if available, in severe attacks. This treatment is likely to diminish the risk of nerve lesions if it is started early.

RAT-BITE FEVER (SODOKU)

Definition. A relapsing type of fever caused by a spirochætal organism called *Spirillum minus*. The spirochæte is transmitted by the bite of a rat, cat or other animal which happens to harbour the infection (*see* Fig. 20).

Distribution. The disease has been well known in Japan for many

History. In 1903 Christy described the disease in East Africa.

In 1904 Ross and Milne discovered spirochætes in the blood of patients in Uganda.

In 1905 Dutton and Todd showed that a tick (*Ornithodorus moubata*) can convey the disease by its bite, and that the infection is transmitted from the ticks to their offspring.

In most of the countries in which the disease occurs a special name has been given to the causative spirochæte, but no clear evidence has been produced that these are different species or that the diseases caused by them differ from each other in any important respect. It appears, therefore, that there is no justification for complicating the study of the disease by giving a separate description of its varieties or for giving different names to the spirochætes concerned in causing them.

The tick-borne disease differs from the louse-borne in the following respects :—

(1) It is not a purely human disease transmitted from man to man by human lice ; in most of the affected regions it is a zootic disease transmitted from lower vertebrates to man, though in some places it is believed to behave as a demic disease transmitted from man to man. In natural conditions it is always transmitted by ticks.

(2) The spirochæte can be inoculated directly into rabbits, mice, dogs, and other animals which are not susceptible to infection by the spirochæte of louse relapsing fever except after passage through monkeys, or new born rats, mice or rabbits.

(3) The geographical distribution is widespread but patchy, and the disease tends to remain persistently in the infected places. Africa, Central Asia, the Middle East, Persia, North and South America and the European countries adjoining the Mediterranean, all have foci of infection, but the disease is less important as a cause of sickness and death than the louse-borne fever.

(4) Epidemiology. The disease is essentially a "place" or "house" disease, the infection persists in the ticks of certain camping places and houses as well as in the open country. Infected ticks can survive up to five years without food ; they remain infective during the whole of this period and some of these can transmit infection to their offspring for an indefinite number of generations, so that it is impossible to rid a place of infection without complete eradication of the ticks. This is difficult ; the ticks lurk in walls, floors, or on the ground, instead of living, as lice do, on the bodies of human beings. The disease does not spread rapidly from place to place ; the ticks tend to remain in certain localities, whereas lice are widely distributed by human travel.

The disease is more common in children than louse relapsing fever, and is also severe in them.

(5) The spirochætes are less numerous in the blood, and the mor-

years, but recently it has been found to occur in most countries of the world.

Ætiology. The spirochæte was first found in human beings by

RAT-BITE FEVER

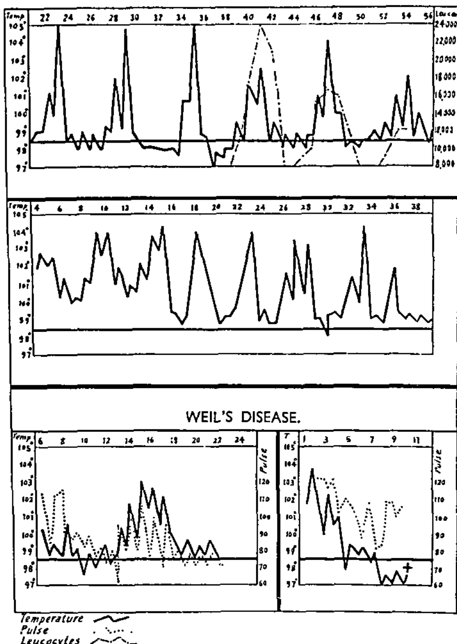


FIG. 21. Temperature charts of rat-bite fever and of Weil's disease.

Futaki in 1916. It had been discovered in rats by Carter in 1887. It occurs in the blood as a short spirochæte of $2\,\mu$ to $6\,\mu$ in length, with two to six curves; longer forms are found in the lymphatic glands; in cultures it may be up to $20\,\mu$ in length. It has an exceedingly

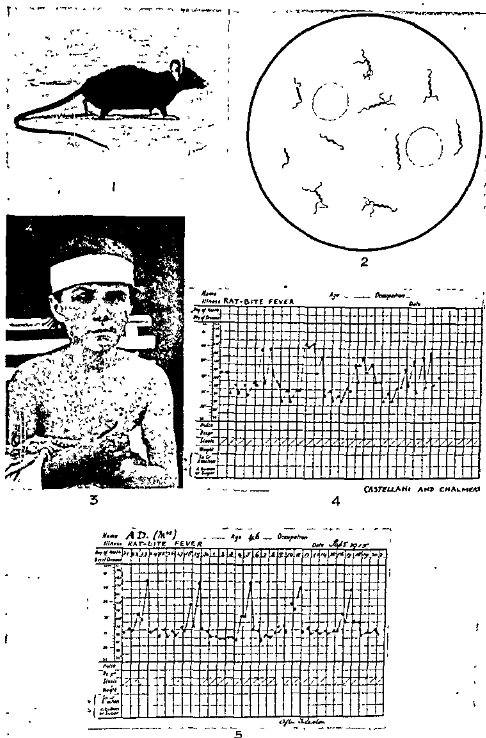


Fig. 20. Rat-bite fever.

1. The carrier rat. 2. Causative *Spirillum minus* in the blood of an infected rat. 3. Patient with ulcer at site of rat-bite and papular nodules on skin. 4 and 5. Temperature charts.

paroxysm or in the fever-free period. Penicillin has been found effective; chloramphenicol and aureomycin are likely to be curative. Streptomycin injections of 0·25 gm. given twice daily for eight days were found effective in one case by H. Floch *et al.* (1950).

Local treatment is of little use, but it is advisable to paint the site of the bite with tincture of iodine. Cauterisation of the bite of a rat immediately after the event may prevent the entry of infection; if this is impracticable, a thorough application of pure carbolic acid should be made. The acid should be rubbed into the depths of the wound by a pointed matchstick round which a thin layer of cotton wool has been wrapped.

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delicate flagellum at each end ; this is difficult to detect, and doubts have been raised as to its existence.

Mice and guineapigs are readily infected by inoculating the blood of patients. The infected animals develop a relapsing type of fever with enlargement of the lymphatic glands ; death occurs after a few weeks and spirochætes are found in considerable numbers in the spleen and lymphatic glands ; they may also be found in small numbers in the blood just before the death of the animals.

The disease is primarily one of rats and other animals ; these form the reservoir of infection from which human beings become infected. About 3 per cent. of the house-rats of Japan have been found infected.

Clinical Features. The bite by the infected animal usually heals promptly ; nothing further happens till two to six weeks afterwards, when the site of the bite becomes inflamed and there is some local lymphadenitis and lymphangitis. About the same time fever sets in suddenly with shivering, headache and prostration ; *the temperature* reaches its maximum of about 103°–104° F. after two or three days. The fever lasts three to five days, then the temperature falls to normal *and there is a great diminution or even disappearance of the symptoms.* The temperature again rises, usually about six to eight days after the onset of the disease, and there is another spell of fever similar to the first. *The periodicity of the fever is of the five- to six-day type in* most of the cases, though irregularities often occur.

The spells of fever, alternating with afebrile intervals, continue for *several weeks or even months, but after a time the attacks become* less and less severe, and then cease altogether.

In some cases there is a macular or petechial rash with the fever ; *occasionally there is urticaria. With each paroxysm of fever there is* pronounced leucocytosis and eosinophilia. Arthritis affecting the elbows and ankles is not uncommon.

Prognosis. *In Japan about 10 per cent. of the cases are fatal.* Elsewhere, for example in Calcutta, deaths are rare.

Diagnosis. The temperature chart, which shows spells of fever recurring at regular *intervals of five or six days, is often characteristic,* but in some cases the fever is not at all regular, and then reliance must be placed on animal inoculations with blood or gland juice from the enlarged gland. *The history of a bite by a rat or cat should arouse* suspicion. Spirochætes can often be found by direct examination of the exudate round the site of the bite, but rarely in the peripheral blood. *Animal inoculation is often needed to confirm* the diagnosis. The disease has to be differentiated from cases in which bites by rats or cats cause infection by a streptobacillus.

Treatment. Neoarsphenamine or a similar type of arsenical preparation has the same action as in relapsing fever, but cases of resistance to the drug are more frequent. The injections should be given early *in the* course of each spell of fever, not at the end of the

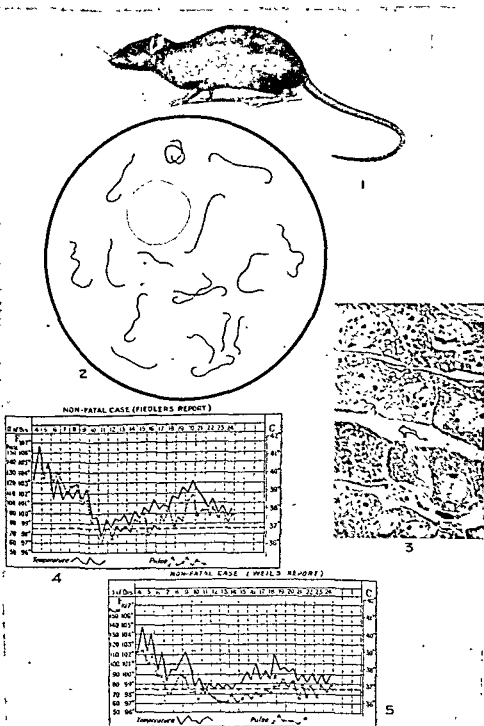


Fig. 22. Weil's disease.

1. Rat infective to man through its urine. 2. *Leptospira icterohæmorrhagiæ* in the blood of an infected rat. 3. *Leptospiræ* in the liver of an infected rat. 4 and 5. Temperature charts of human cases.

CHAPTER V

THE LEPTOSPIRAL FEVERS OR THE LEPTOSPIROSIS GROUP OF FEVERS

THE chief fever caused by the spirochætal organisms called leptospiræ is Weil's disease, first described in 1886. Its cause, *Leptospira icterohæmorrhagiæ*, was discovered by Inada and Ido in 1915.

Within the past few years a number of other leptospiræ have been found to be the causes of fevers in many parts of the world. These fevers are usually short and mild ; they long escaped recognition because the leptospira was not revealed by routine laboratory methods.

All the leptospiral fevers have certain features in common, and a good working knowledge of their diagnosis and management can best be obtained by regarding them as belonging to a group of which Weil's disease is the classical type.

Their common characteristics are : (1) the cause is a leptospira ; (2) they are primarily diseases of lower animals, chiefly rats, but sometimes of other rodents, dogs, cats, etc. ; (3) the chief clinical features are a fever with sudden onset, of varying duration and severity, accompanied by a polymorphonuclear leucocytosis. Jaundice is common in severe attacks.

They can be distinguished from each other with certainty only by laboratory tests, especially by agglutination reactions. For practical purposes the important matter is to differentiate Weil's disease from the others. Weil's disease is usually longer and more severe, jaundice is common, and hæmorrhages may occur ; yet a mild attack of Weil's disease does not differ clinically from a severe attack of one of the other leptospiral fevers.

WEIL'S DISEASE

Synonyms. Spirochætosis icterohæmorrhagica, infective jaundice, spirochætal jaundice, Weil type of leptospirosis.

Definition. A fever caused by *Leptospira icterohæmorrhagiæ* which is transmitted to man from an infected rat or other animal.

History and Distribution. The disease was first described by Weil in 1886 ; its cause was discovered by Inada and Ido in 1915. It is most common in Japan, but is of world-wide distribution. It occurs sporadically or in local outbreaks. Many cases occurred among the soldiers in the trenches in the 1914–18 war. Outbreaks may occur in schools or other institutions. Sewer workers, miners, and others who are brought into close association with rats, are specially liable to attacks.

In cold countries it is most common in the warmer months of the year ; in Japan it is most frequent from September to November.

urticarial rash at a later stage. The conjunctivæ are often injected. The muscular pains may be very severe.

Leucocytosis is a feature of the disease. The total white corpuscles range from 10,000 to 20,000 ; and 80–90 per cent. of these are polymorphonuclear. Later there may be lymphocytosis.

The liver and spleen are often enlarged during the fever. The pulse is rapid at first, but later it may be slow in relation to the temperature. Other diseases may be simulated, such as influenza, peritonitis, rheumatic fever, pneumonia, meningitis, typhus fever and yellow fever. In cases in which jaundice is absent and also in mild attacks mistakes in diagnosis are very frequent ; indeed, it is likely that the majority of cases seen by medical men are completely missed. Convalescence is rather slow except in mild attacks ; anæmia and debility may persist for weeks after the end of the fever.

Diagnosis

The first essential in diagnosis is the arousing of suspicion. Sporadic cases will rarely be recognised unless the disease is kept constantly in mind. The history of contact with material soiled by the excreta of rats or of bathing in water frequented by rats should suggest leptospirosis if the symptoms conform to one of the many forms of the disease.

In all suspected cases it is advisable to inject 2–4 c.c. of the blood intraperitoneally into a young guineapig or mouse, and then to keep careful temperature records of the animal. If fever occurs, smears should be made from the liver and spleen of the animal at the height of the fever and further sub-inoculations should be made. The inoculated animals usually die.

After the seventh or eighth day, it is better to use the urine of the patient for animal inoculation, as the spirochætes tend to disappear from the blood ; the urine should be centrifuged with rigid aseptic precautions, and great care must be taken to avoid contamination with spirochætes normally present in the smegma. Culture methods are difficult and cannot easily be carried out in ordinary practice, but guineapig inoculation is a simple means of investigating doubtful cases.

Schüffner has worked out an agglutination test using formolised cultures of leptospiræ : the test is highly specific and reactions can be obtained for months, or even years, after the attack.

Apart from the above methods, the diagnosis must often be a matter of surmise and speculation, especially in mild sporadic cases.

The diseases which are likely to be mistaken for Weil's disease are :—

(1) *Yellow Fever.* The clinical resemblances between the two diseases may be so great that nothing short of an expert laboratory test will suffice, but difficulty will only rise in localities in which ...ever occurs.

The Leptospira. This is a very slender spirochætal organism; it is so scanty in the human blood that it can rarely be detected in smears, but it is abundant in smears made from the livers or kidneys of inoculated rats, guineapigs, etc. Its usual length is 6 μ to 9 μ with two or three curves, but shorter or much longer forms may be seen. It can be cultivated on media containing blood serum, or in the yolk sacs of developing chick embryos. It stains well with Giemsa's stain or by silver-impregnation methods.

Mode of Infection. The disease is chiefly one of rats, but mice, rabbits, and other rodents, may be infected. As many as 40 per cent. of the rats in certain Japanese mines harbour spirochætes. London rats have been found infected to the extent of 30 per cent. Infection enters the body through skin abrasions, the conjunctivæ, or mucous membranes of the nose, mouth, or stomach. Handling of soil or sewage contaminated by rats, or swallowing water of rat-infested baths, ponds, etc., are sources of infection. Bites by infected rats may also convey the disease. In some cases the handling of cultures of the organism has caused the disease.

The post-mortem findings so closely resemble those of yellow fever that only an expert can detect any difference.

Symptoms

The disease is exceedingly variable in severity; it may be a short mild fever of a few days' duration, but often it lasts for two to four weeks.

The incubation period is from six to twelve days as a rule.

The ONSET is sudden, with rapid rise of temperature, headache, shivering, pains in the joints and muscles; sometimes there is vomiting and diarrhœa. The temperature continues to rise and the symptoms increase till about the fourth or fifth day, after which the temperature usually begins to fall by lysis or crisis, normal being reached in a week to ten days. In mild cases the fever may last only three to five days.

Usually there is only one spell of fever, but in a few cases a second spell begins about the thirteenth to the fifteenth day. The second spell of fever tends to be less severe than the first. Third spells are rare (*see* Fig. 22, Charts 4 and 5).

The special features are:—

Jaundice occurs in about 50 per cent. of the cases; it begins on the third to the fifth day and gradually increases in intensity. In cases with jaundice the urine is albuminous and bile-stained, usually to a degree proportional to the intensity of the jaundice. A tendency to hæmorrhage is a feature of some severe cases, especially of those with pronounced jaundice. Skin petechiæ, epistaxis, and melæna, are the most frequent forms of hæmorrhage. The petechiæ usually appear about the third to the fifth day; there may be a measly or

of being caused by leptospiræ and should be investigated on the same lines as Weil's disease. If a fever is found to be caused by a leptospira it is of secondary importance to determine which species of the organism is concerned, but an attempt should be made to find the source of the infection so that control measures may be carried out.

JAPANESE SEVEN DAYS' FEVER

Apart from Weil's disease this is the best known of the leptospiral fevers; it is caused by *Leptospira hebdomadis*, discovered by Ido, Ito and others in 1917.

It is primarily a disease of field mice whose urine infects the soil, so that field workers are specially affected. Infection is conveyed in the same way as in Weil's disease. The fever lasts about seven days in most of the cases. There is leucocytosis, occasionally also jaundice and albuminuria. The mortality is almost nil.

This fever, owing to the similarity in name, has been confused with the seven-day type of dengue, but obviously it is a totally different disease.

From the clinical point of view this fever can be regarded as Weil's disease in a mild form in which jaundice and severe symptoms are exceptional.

From the Dutch East Indies and many other countries leptospiral fevers have been reported; these differ from Weil's disease in being shorter and milder on the average, though fatal attacks have been reported.

Their average mildness is due to the lower virulence of the causal leptospiræ, and there are minor differences between the various types, such as the greater frequency of jaundice in some than in others.

The duration of the fever is usually two to six days, though in some cases the fever has lasted as long as ten to twelve days.

Examples of the leptospiræ isolated from these fevers are: (1) *Leptospira autumnalis*, from field mice in Japan and Dutch East Indies; (2) *L. pyrogenes*, from rats in Australia and Dutch East Indies; (3) *L. grippotyphosa*, from Europe and the Andamans; (4) *L. canicola*, from dogs in various countries; (5) *L. bovis*, from cattle in Canada, U.S.A. and Australia.

All the above leptospiral fevers are likely to be confused with dengue or sandfly fever; the epidemiological conditions in which they occur and the presence of leucocytosis instead of leucopenia are the chief points by which they can be differentiated from the short virus fevers.

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(2) *Relapsing fever* may be simulated, but in that disease spirochætes will be found in considerable numbers in the peripheral blood during the fever. They are rarely seen in smears in cases of Weil's disease, and when seen they are very scanty.

(3) *Dengue and Sandfly Fever.* These can be excluded by the occurrence of leucocytosis in the short attacks of Weil's disease, which are the only ones likely to cause confusion.

(4) *Non-spirochætal febrile jaundice* or *infective hepatitis* may give rise to difficulty ; in it the animal inoculation test will exclude leptospirosis.

Prognosis

The average mortality is usually about 5–10 per cent. ; in Japan it has been nearly 50 per cent. in some outbreaks. Elderly patients tolerate the disease badly. Absence of jaundice is favourable.

Treatment

Penicillin in large doses has been found very effective when given early, before serious damage has been done to the liver. Aureomycin is regarded as being likely to have a specific action. The serum of convalescents or of immunised horses may be of value if available.

Symptomatic treatment is on the usual lines ; no exertion should be permitted till the temperature has been normal for a week. The milder cases do not call for any special line of treatment beyond rest in bed and a milk diet.

Prevention

Rat extermination, avoidance of handling the soil of infected places, disinfection of the hands before eating, and avoidance of bathing in contaminated baths, ponds or rivers are the chief measures.

Sewer workers are exceptionally liable to the disease : protective inoculation with killed cultures should be considered in the case of persons exposed to exceptional risk of infection.

OTHER LEPTOSPIRAL FEVERS RELATED TO WEIL'S DISEASE

As stated at the beginning of this chapter, several other fevers have been described which are closely related to Weil's disease. These have been most closely studied in Japan, the East Indies, Australia and Holland, but they are known to occur in many other countries ; they probably have a world-wide distribution and are often missed because suspicion of their existence has not been aroused. They are specially likely to be overlooked in countries in which dengue and sandfly fever occur, and they have often been placed in the category " P.U.O." (pyrexia of unknown origin).

The important practical point is that cases of otherwise unexplained short fever accompanied by leucocytosis should always be suspected

This was the first time that a clear statement was made of the hypothesis of direct transmission of a disease from man to man by the bite of an insect. Manson and others had already incriminated mosquitoes as vectors of filariasis and malaria but none of their hypotheses included both the infection of the insect by biting and the transmission of the infection by the bite of the same insect.

In 1898 H. R. Carter observed *that a period of two to three weeks* elapsed between the onset of the first case in a locality and the appearance of the second crop of cases. He argued from this that the virus in the mosquito must pass through a cycle of development

THE CHIEF INSECT-BORNE FEVERS CAUSED BY FILTER-PASSING VIRUSES

	Yellow fever	Dengue	Sandfly fever
Insect vectors	Mosquito	Mosquito	Sandfly
Primary source of infection.	Man or lower animal.	Man.	Man.
Period of greatest infectivity in man.	First 3 days.	First 3 days.	First 2 days.
Usual incubation of virus in insect.	1 to 2 weeks.	1 to 2 weeks.	1 to 2 weeks.
Usual incubation of fever in man.	4 to 7 days.	5 to 8 days.	3 to 7 days.
Distribution . .	Tropical Africa and America.	Widespread, chiefly tropical.	Widespread, chiefly subtropical.
Lethality . . .	High.	Very low.	Very low.
Jaundice and [albuminuria.	Usually present.	Rare	Rare.
Usual duration of fever	4 to 8 days.	3 to 7 days.	2 to 5 days.
Two-phase fever curve	Occasional.	Common.	Unusual.
Rash . . .	Rare.	Frequent (5 to 100 per cent.).	Unusual (0 to 10 per cent.).
Immunity after attack	Lasting.	Usually short.	Usually short.

similar to that recently discovered by Ross in the case of the malaria parasite.

In 1900 the American Commission, whose members were Walter Reed, Carrol, Agramonte and Lazear, made the following discoveries :—

(1) The disease is conveyed by stegomyia (aëdes) mosquitoes.

(2) The insect becomes infective if it bites a patient during the first three days of the fever ; if it bites at a later stage it does not become infective.

(3) After biting an infected person the mosquito cannot transmit the disease to another person till about twelve days have elapsed, but after this period the insect remains infective for the rest of its life. (This incubation period is now known to range from eight days or even less to twenty-eight days, according to temperature and other conditions.)

(4) The blood of a *yellow fever patient, if drawn during the first* three days, causes the disease when injected into a susceptible person ;

CHAPTER VI

YELLOW FEVER

Definition. A short fever caused by a special filter-passing virus which is transmitted to man by the bites of mosquitoes infected either by biting infected persons or by biting infected lower animals. The disease is often highly lethal, but milder, or even subclinical, forms are probably common.

Relationships. Yellow fever, dengue and sandfly fever are related to each other in the following respects: (1) they are insect-borne; (2) they are caused by filter-passing viruses; (3) they are short fevers with sudden onset; (4) they are most infective to the vector insects during the first two or three days of the fever, probably also during the last day of the incubation period; (5) the vector insects become capable of transmitting infection about eight to twelve days after swallowing blood containing the virus; they remain infective for the rest of their lives; (6) the incubation period of each disease is usually four to eight days; and (7) they occur as rapidly spreading epidemics when conditions are suitable.

The similarity of yellow fever to dengue is specially striking, but yellow fever differs from both dengue and sandfly fever in being often a highly lethal disease, so that it has come to be regarded as being in a class by itself. Its high virulence does not necessarily indicate that the disease belongs to a different group; strains of the virus of yellow fever have been produced artificially which cause a milder disease than either dengue or sandfly fever, and such mild strains are believed to occur sometimes in natural conditions. The essential difference between yellow fever and the other two diseases lies in the immunological properties of its virus.

The table on p. 117 shows the striking points of analogy between the three chief insect-borne virus diseases; it will help the student to obtain a clear mental picture of the relationships that exist between them.

History. The disease must be of great antiquity. According to G. M. Findlay, it was introduced to the Western Hemisphere in 1647 by ships sailing from West Africa to Barbados. In the same year quarantine was introduced for the first time by the State of Massachusetts against all ships arriving from any part of the West Indies.

Since then there have been many great epidemics in tropical America, including one in 1802, in which only 7,000 of a French army of 30,000 survived during an expedition to San Domingo.

In 1881 Carlos Finlay of Havana maintained that the disease was conveyed from man to man by the bites of mosquitoes; he actually incriminated *Aëdes ægypti*, which is now known to be the chief vector.

though in the past there have been a few extensions to sub-tropical and even temperate climates.

A curious feature of yellow fever is that it has never spread to Asia or the Far East, although there are many areas in these countries in which conditions appear to be favourable for the spread of infection.

Till a few years ago it was believed that the disease could be con-



FIG. 24. Endemic yellow fever area in America. (Delineation recommended by the W.H.O. Yellow Fever Panel.) (By courtesy of the World Health Organisation.)

veyed solely by *Aëdes ægypti* which is nearly always a domestic mosquito. The efforts of the Rockefeller Foundation were therefore directed to the control of this mosquito in the urban localities in which yellow fever was known to occur. Complete success followed so that about the year 1927 it was possible to claim that not a single case of yellow fever had been reported in the American Continent during a period of eleven months. Shortly afterwards cases of yellow fever were detected in forest areas where no aëdes mosquitoes existed, and

even after being passed through a Berkefeld filter the serum is still infective, therefore the virus is filterable.

(5) The virus is killed when heated to 55° C. for ten minutes.

(6) The disease cannot be conveyed from man to man by intimate contact or by fomites, but only by the bite of an infected mosquito.

These findings hold good up to the present time, and apart from a few additional pieces of knowledge they can serve to-day as a statement of the ætiology of the disease.

In 1928 Stokes, Bauer and Hudson found that rhesus monkeys were susceptible, and Hindle introduced a vaccine prepared from carbolised suspensions of the livers of infected monkeys.

In 1930 M. Theiler prepared an attenuated virus by repeated passages through the brains of mice.

Most of the recent important advances have been due to the workers of the Rockefeller Foundation, including Sawyer, Lloyd and Soper. These advances are chiefly in connection with (1) the development of a safe living vaccine by means of which millions of people have already been protected; (2) the development of the mouse-protection test; (3) the use of the viscerotome in detecting foci of infection; (4) the discovery of the "jungle" form of the disease; and (5) in collaboration with European and British workers, the charting of the limits of distribution of the disease in Africa.

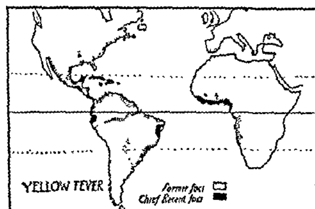


FIG. 23. Map of the distribution of yellow fever as known till 1930.

Importance of the Disease. Although yellow fever is now restricted to certain parts of South America and Africa, it is of interest to the whole world, especially to the tropical world. The story of the discoveries connected with the disease is one of heroic struggle on the part of medical scientists, many of whom have sacrificed their lives in the battle. Lazear, Stokes, Noguchi and Young are among those who died of the disease while engaged in the search for its secrets.

Geographical Distribution. The dotted areas in Fig. 23 show the places in which yellow fever is known to have occurred during the eighteenth and nineteenth centuries, the black spots show the chief foci in which the disease was recognised between 1900 and 1930.

Except for minor outbreaks in other places, the disease, till a few years ago, was only known to exist on or near the coasts of America and West Africa. The disease is essentially one of tropical regions

heavily infected, the eastern part has only a few foci of obvious infection.

The great outbreak in 1940 in the Nuba mountains of the Anglo-Egyptian Sudan is a good example of the sudden appearance of the disease in places where no cases had previously been recognised, though in this area the presence of infection had been suspected because of positive reactions to the mouse-protection tests carried out a few years previously. This test has thrown a flood of light on the occurrence of the disease in areas in which its presence has not been detected. The test is based on the discovery that the serum of a person who has had yellow fever, when injected into a young mouse, protects the animal from a dose of the virus which would otherwise be fatal. This test can even disclose the previous existence of yellow fever in places from which it has disappeared for several years ; for example, if a number of persons of fifteen years old and upwards give positive results to the test whereas all the children of less than fifteen years old are negative, it can safely be assumed that the disease has died out fifteen years previously.

When a number of positive reactions are observed in places where no cases have ever been detected the probable explanation is that the disease has been occurring in a mild form. There is, therefore, reason to believe that classical yellow fever may be the severe form of a disease of variable virulence.

An interesting piece of evidence of the existence of the disease in mild endemic form has been provided by Atkey, who in one year found that 18 per cent. of the people of Malakal were positive to the mouse-protection test, although four years previously all had been negative, yet no cases of the disease were reported in the interval between the two sets of tests.

Seasonal Distribution. The disease occurs during hot and moist weather when the vector mosquitoes abound. In most of the tropical countries the conditions are favourable all the year round, but in cooler climates the mosquitoes are active only during the hot season.

Ætiology and Epidemiology. The chief ætiological features have been mentioned in the historical section. Various monkeys and mice are suspectible to inoculation. By passages through the brains of mice the virus becomes attenuated and so can be used as a living protective vaccine for human beings. The attenuation of the virus usually persists indefinitely in successive passages through mice. The strain now used by American workers is tested repeatedly and is also passed through a large series of cultures in the yolk sacs of developing chick embryos.

The virus cannot be cultivated on ordinary media, but only in tissue cultures or in the yolk sacs of living fowl embryos ; the presence of living cells is essential.

by 1934 the Rockefeller Foundation workers discovered " jungle yellow fever " and found that it was a widespread disease in forest regions in every country of South America north of Argentina. The number of cases cannot be estimated with any degree of accuracy, but Soper believes that there were more than 15,000 in 1937–38 in South America.

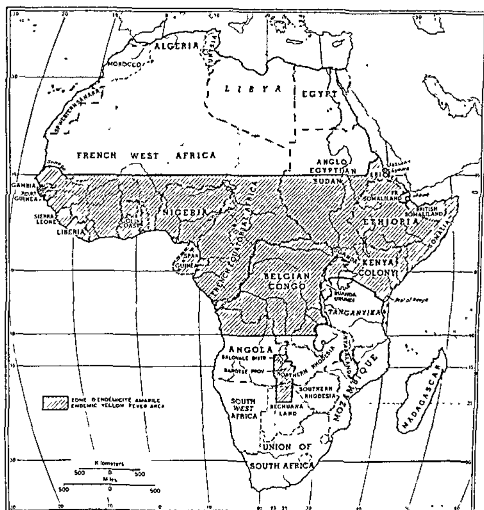


FIG. 25. Endemic yellow fever area in Africa (Delineation recommended by the W.H.O.)

Note: This area has since been modified by the inclusion of Tanganyika Territory and by the exclusion of Nyasaland and that part of Bechuanaland referred to. (Courtesy of the World Health Organisation.)

These areas are shown in Fig. 24. Several species of mosquito have been found to be naturally infected in Brazil.

In Africa, where the disease was formerly considered to be restricted to the West Coast of Tropical Africa it is now known to have a widespread distribution over a wide belt whose northern boundary is a line running along the south of the Sahara Desert and its continuation through the Anglo-Egyptian Sudan. The southern boundary is irregular and ill-defined as shown in Fig. 25. The western part of the belt is

and the conditions of life would be more pleasant if the mosquito nuisance were abolished.

Immunity. An attack is believed to confer lasting immunity, probably for life in most cases. The occurrence of a second attack has never been authenticated and evidence of the presence of immune bodies in the blood has often been obtained many years after an attack. The possibility of a gradual weakening of the immunity, especially after infection of low virulence, cannot be ruled out.

Morbid Anatomy. The dead body is yellow and livid. Usually there are ecchymoses in every part of the body that has been subjected to pressure or bruising during life.

The gastric mucosa has patches of congestion and punctate hæmorrhages ; the duodenum may be affected in the same way. The contents of the stomach are black, owing to the presence of altered blood.

The liver is in a condition of " yellow nutmeg liver."

The kidneys are yellow and congested, the heart is yellow and flabby. The adrenals often show the changes associated with fatty degeneration. There are perivascular hæmorrhages in the brain.

The most striking microscopical changes are in the liver cells which often show intense fatty degeneration, and intranuclear bodies which are regarded as characteristic. Some experts claim to be able to make an absolute diagnosis by examining stained sections made from portions of liver removed by a special instrument called a viscerotome. The use of the viscerotome has greatly extended the possibility of diagnosis after death as it does not necessitate any mutilation of the body and so material for examination can be obtained in many cases in which objections would be raised to a complete post-mortem investigation. The viscerotomy service in Brazil dealt with material from more than 140,000 dead bodies between 1930 and 1941.

Clinical Features

Incubation Period. This is usually four to seven days, but it may be as short as two days or as long as eight or even nine days.

Onset. This is sudden, with chill, pains in the back and limbs, flushed face, injected conjunctivæ, and a rapidly rising temperature. It often resembles the onset of influenza, dengue, and other fevers.

Fever Curve. The types of fever curve are best studied from the charts. The general resemblance to the curves seen in dengue is striking though the two-phase type is less common in yellow fever. (*See* Fig. 26, Charts 1 to 12.)

(1) There may be a short single spell of fever lasting three or four days ; this is seen in the mildest cases.

(2) There may be a fever spell lasting three or four days, the curve declining during the third and fourth day, but seldom reaching the normal line ; then comes a secondary rise of temperature about the

The virus is the same in all forms of yellow fever, though different strains vary greatly in virulence.

The chief differences between classical and jungle yellow fever are shown in the table.

	Classical Yellow Fever	Jungle Yellow Fever
Other names	*Urban and rural yellow fever, human or demic yellow fever.*	*Animal or zootic yellow fever, sylvan yellow fever.*
Places affected	Towns, villages and hamlets.	Forests and camps.
Chief vectors	*Aëdes ægypti* and other aëdes mosquitoes.	Various species of mosquitoes besides aëdes.
Mammalian reservoirs of infection	*Man only.*	*Monkeys and other animals; man exceptionally.*
Transmission	Man to man only.	Lower animal to man is the chief method.
Epidemicity	Epidemic or endemic. Often spreads rapidly.	Chiefly sporadic and restricted to certain localities.

An important point is that a person suffering from jungle yellow fever can infect aëdes mosquitoes in any place where he happens to be during the infective stage of his disease so that urban yellow fever can be introduced to a town or village by a person who has recently arrived from an infected jungle area.

Why has yellow fever remained restricted to part of the area in which the vector mosquitoes occur and all the other conditions of transmission appear to be suitable for the spread of the disease ? This very important question still awaits a satisfactory reply. It may be that some unknown factor prevents transmission in the parts of the tropics which have hitherto remained free from the disease, or it may be that the virus has never been introduced into these countries.

Hindle has found that *Aëdes ægypti* sent from India can transmit the disease in experimental conditions, and as this mosquito is an abundant and effective vector of the related virus of dengue there is every reason to fear that the introduction of the virus of yellow fever to India and the Far East might cause devastating epidemics. Up to the present time there has been an effective barrier of some kind to the spread of the disease to the East ; *the danger lies in the breaking down of this* barrier by the development of rapid methods of transport by land, sea, and especially by air.

India, South and North Africa and the southern parts of North America are the places most directly threatened with extension of the disease ; elaborate precautions have been taken to prevent the spread of infection, but these are liable to break down ; the best safeguard will be the *elimination* of aëdes mosquitoes, not only in the countries already infected but also in those likely to be invaded.

The elimination of aëdes mosquitoes is a sound policy apart altogether from the threat of yellow fever ; dengue would also be controlled,

followed by a fresh access of fever which constitutes the second period of the disease." The older writers divided the disease into three stages which correspond to the phases of the temperature. They are the stage of "congestion" or "inflammation," the stage of "remission," while the temperature is relatively low, and the stage of "reaction" or the "adynamic" stage, during which the temperature again rises. The reaction stage is the most critical period. Most of the deaths occur on the fifth, sixth or seventh day of the disease.

Cardio-vascular Features. At first the pulse is 100 to 120, but from the second or third day it becomes slow relatively to the temperature, except in fulminating cases in which it may remain rapid till the end. The pulse rate may fall to 40 or so, just after the fall in the temperature. A falling pulse rate combined with a rising or constant temperature is known as Faget's sign. A rising pulse rate with a falling temperature is of bad omen.

Jaundice. This may be absent in the mildest cases ; it usually appears about the third or fourth day, but may be detected as early as the second day in severe cases. The earlier the jaundice the worse the outlook for the patient. A slight icteric tint may be noticed on the first day, but unless this is pronounced it need not cause alarm.

Albuminuria. Albumen can be detected in the urine by the second or third day in severe cases ; the degree of albuminuria corresponds fairly closely with that of the jaundice, and just as early jaundice is a feature of severe cases, so is early and intense albuminuria. Even more important is the quantity of the urine ; when this is very scanty the outlook is grave.

Gastro-intestinal Features. Nausea or vomiting at the onset are of little importance ; they are common in yellow fever as in most acute fevers. If vomiting persists, or recurs after the third or fourth day, it becomes a matter of grave concern ; when the vomit is "coffee-ground" or black the prospect of recovery is slight ; the dark colour is due to altered blood and indicates that hæmorrhage is taking place into the stomach.

Nervous System. Severe headache and pains like those of dengue are usual, but these symptoms may be slight or absent.

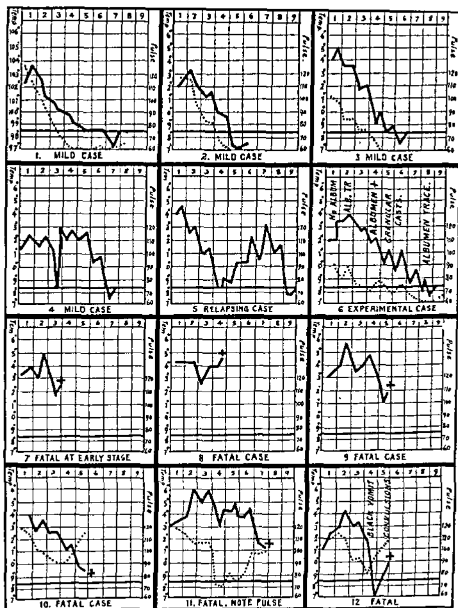
Delirium is not common except in severe cases ; insomnia and restlessness are usual features.

Blood. Leucopenia may occur, especially in mild attacks, in severe cases leucocytosis, up to 15,000, is usual ; a great increase in the leucocytes suggests a severe attack or the presence of secondary infection.

Hæmorrhages occur in most of the severe cases. The tendency to hæmorrhage is most easily observed in the gums, which should be watched carefully from the beginning of the disease. Bleeding may take place into any part of the body, but the stomach, gums, bladder, nose, eyes and rectum are the organs most commonly affected. In

fifth day ; if the patient recovers, a rapid fall to normal or subnormal occurs on the seventh to the tenth day as a rule.

Types of Temperature Chart in
YELLOW FEVER



Temperature —— Plain line
Pulse .... Dotted line

FIG. 26. Charts illustrating types of temperature in yellow fever.

(3) The temperature may remain high throughout the course of the disease, but a two-hourly chart will show distinct remissions.

Le Dantec's description of the general course of the fever is : " It consists of two febrile periods separated by a remission. The remission occurs on the third or fourth day ; it is of short duration, and is soon

areas are included the death rate may be as low as 5 per cent. Old people are likely to die when attacked; the disease is often mild in children, but may be severe or fatal even in them.

Unfavourable features are, early albuminuria and jaundice, a temperature remaining long above 104° F., great diminution in the quantity of the urine, black vomit or other hæmorrhages, delirium, coma, and great increase in the leucocytes.

Special care should be taken during the stage of remission, when the patient may feel much better and so be tempted to take liberties: cases have occurred in which patients have eaten heartily during this stage, and yet have died a few hours later.

After the second fall of the temperature a further rise is rare, so that when the temperature has reached normal after the seventh day there is good reason to consider that the attack is over, but relapses occur from the eighth to the thirteenth day in exceptional cases.

Treatment

No drug has yet been found to have any curative value.

The lines of treatment are: (1) Complete rest till convalescence is thoroughly established.

(2) Mild laxatives in the early stages of the disease; if the patient is not seen till three or four days after the onset, purgatives of any kind are harmful.

(3) Plenty of water should be sipped by the patient; a little citrate or bicarbonate of soda should be added to the water. If vomiting prevents the patient from retaining water, alkalies should be given by the rectum as recommended in cases of cholera. The addition of calcium chloride to the rectal saline is believed to be of value. Calcium citrate can also be given by the mouth. For severe vomiting, ¼ grain of cocaine in an ounce of water may be helpful. Ten minims of adrenaline solution in a little water can also be tried.

(4) Dry cupping or hot fomentations over the kidneys are useful when anuria threatens.

(5) When the temperature rises above 103·5° F., cold sponging is necessary.

(6) No food need be given during the first two or three days of the fever, apart from glucose solutions, whey, or barley water; later, diluted and citrated milk can be given. Solid food is withheld till convalescence is established and at first is given cautiously.

(7) The serum of convalescent patients who have been known to be healthy before their attack, and who have passed through an uncomplicated illness, may be tried; but there are so many pitfalls that this line of treatment should not be carried out indiscriminately. A serum prepared from immunized monkeys or horses may turn out to be useful if available, and if given early.

(8) Great care must be taken to avoid exertion during convalescence.

fatal cases hæmorrhages often form a distressing feature of the disease, and the last hours of the patient's life may be a horror to himself and his attendants.

Diagnosis

In an epidemic the diagnosis is easy, but in isolated mild cases it may be difficult or impossible without a laboratory investigation by an expert.

Yellow fever can be ruled out in the countries which are known to be free from the disease ; on the other hand, it must be regarded as of possible occurrence in certain localities in Africa and South America where its existence was not suspected till recently.

The mouse-protection test does not help in diagnosis during an attack of the disease ; it does not become positive till convalescence has been established. A positive reaction merely shows that the person has had yellow fever at some time. When possible the test should be carried out during the acute stage if the disease is suspected, because if negative at that time and positive afterwards, the finding is strong evidence that the attack was one of yellow fever. A positive result after an attack is diagnostic if the patient had never been exposed to the risk of infection at any former time, otherwise it is of doubtful significance.

Mild attacks may be mistaken for **influenza, dengue, or sandfly fever.**

Severe cases of **Weil's disease** may be very difficult to distinguish from yellow fever unless expert investigation can be carried out.

A historic example of this mistake was that of the physicians who diagnosed yellow fever in the cases from which Noguchi isolated "*Leptospira icteroides.*" The responsibility for the mistaken claim of the discovery of the cause of yellow fever rests with those who made the wrong diagnosis, not with Noguchi who was not a physician.

Leptospirosis can be excluded by guineapig inoculation.

Measles can be excluded by Koplik's spots and the pronounced catarrhal symptoms ; later by the rash.

In **Black-Water Fever** there is hæmoglobinuria, not hæmaturia.

Prognosis

The severity of the disease is extremely variable ; it depends chiefly on the degree of virulence of the infection, the age and previous state of health of the patient.

Europeans and other new-comers to endemic areas are likely to get severe attacks ; in some outbreaks half of the immigrants have died of the disease shortly after their arrival in the infected area.

The mortality may be as high as 80 per cent., but as a rule it ranges from 15 to 30 per cent. among Europeans. Among indigenous populations the disease tends to be mild. If all the slight cases in the endemic

which jaundice was the most striking symptom. The onset of this mysterious infection was after an incubation period of one to six months, and although it is now known to occur apart from inoculations with serum, there were so many cases in vaccinated persons that there was no doubt about its being a result of the vaccination.

With the present vaccine the only reaction is a short spell of headache, slight pains and feverishness, a few days after the injection. There is seldom any incapacitation for work. A very satisfactory degree of immunity is produced, lasting at least four years. A gradually diminishing immunity probably persists for an indefinite period, similar to that caused by an attack of the disease. In fact, the effect of the inoculation is to cause a very mild attack of yellow fever, and fortunately it has been shown experimentally that aëdes mosquitoes cannot become infected by biting inoculated persons even at the height of their reaction so that there seems to be no risk of introducing the disease to the place where vaccination is carried out, even if vector mosquitoes are present.

The French vaccine, made from a virus attenuated by passage through the brains of mice, keeps better and can be applied by scarification of the skin ; unpleasant reactions, however, are more frequent.

For **Jungle Yellow Fever** systematic vaccination of the whole population is usually the only practicable method of control, but destruction of mosquitoes and the customary measures of protection against the bites of the insects are desirable when they can be carried out.

In the campaign against yellow fever of the jungle type in South America great importance is attached to the detection of the disease by the histological examination of pieces of the liver removed by the viscerotome from the bodies of all persons who have died of fever within eleven days after the onset.

By this means foci of infection are detected earlier than is possible in any other way.

The prevention of the spread of infection from known or suspected areas of infection is the subject of elaborate regulations prescribed by an International Sanitary Convention, and strictly enforced by countries which fear the introduction of the disease by infected persons or mosquitoes arriving by aeroplane or other methods of transport. The methods employed vary to some extent in different countries.

Hitherto there has been no extension of the disease to the countries east of Africa in which conditions appear to be suitable for the spread of infection, but no relaxation of the precautionary measures now in force in these countries should be permitted so long as Africa and South America continue to be infected.

J. W. D. MEGAW

(9) For black vomit repeated doses of perchloride of iron are recommended.

Prevention

For **Urban Yellow Fever** the ideal method is the elimination of aëdes mosquitoes *by controlling their breeding places, which, for the* most part are in, or near, human dwellings.

Towns, villages and hamlets can be kept free from risk of infection by the effective control of the breeding grounds of aëdes mosquitoes throughout the inhabited area. This control may be a simple matter when the inhabitants of the area are willing to co-operate in an intelligent manner by getting rid of all collections of standing water or, when this is impossible, by treating them weekly with oil containing 2·0–5·0 per cent. D.D.T. Usually it is necessary to establish a special organisation with a staff of persons trained in the detection of the potential breeding grounds and armed with power to compel the people to comply with the necessary regulations dealing with the elimination or protection of all potential breeding grounds. Generally speaking the measures suitable for dealing with the vector mosquitoes of malaria are equally applicable for the control of aëdes mosquitoes, but special attention must be paid to small and easily overlooked collections of water such as those in discarded tins and tree-holes. Cisterns should be protected by wire-gauze covers, and domestic water vessels must be emptied once a week. Effective screening of houses is desirable and so is the use of mosquito nets, but it must be remembered that aëdes mosquitoes bite by day as well as by night.

When yellow fever is known or suspected of occurring, every one in the affected area, especially persons who are suffering from fever, must use mosquito curtains.

Spraying of all houses in the affected area with D.D.T. should be carried out.

Protective inoculation is essential for all who have to visit, or live in, localities where the disease is likely to occur.

The vaccine now in use consists of a living attenuated culture of the virus which has been passaged many times through the yolk sacs of the developing embryos of chicks. The same strain of virus has been in use for a long time, it is subjected to repeated tests for safety and potency by inoculations into monkeys. It is supplied in the dried condition in ampoules which have to be kept in cold storage till it is used. *The dry vaccine is mixed with saline and injected immediately.*

Up to the present no unfavourable reactions have been reported in any of the very large number of persons who have been vaccinated with the new vaccine.

With the earlier types of vaccine the virus was mixed with human serum, and *certain* batches caused an appreciable percentage of attacks of infective hepatitis, a troublesome and occasionally fatal disease of

(4) There is no leucocytosis in uncomplicated cases, but usually a progressive leucopenia.

STORY OF AN ATTACK OF DENGUE



A stegomyia mosquito bites a dengue patient during the first three days of his illness.

I. THE MOSQUITO PHASE

The mosquito at first is not capable of conveying infection



After about 11 days the mosquito becomes infective and remains so for the rest of its life

The infected mosquito bites a susceptible person

II. THE INCUBATION PERIOD

The incubation period is usually 5 to 7 days

III. THE ATTACK



The Rash

Onset sudden with pains in back and limbs also over eyeballs, face and neck flushed

Pains increased, throat congested, post cervical and epitrochlear glands enlarged

Restlessness. Moderate leucopenia

Patient free from pain, but feels weak

Measly rash appears. Pains return

Temperature falls, rash fades

Rapid convalescence

FIG. 27. Story of a typical attack of dengue.

(5) There are no local manifestations of the kinds that occur in most cases of short fevers caused by bacterial infections.

(6) Deaths do not occur among previously healthy persons.

(7) Albuminuria, jaundice and hæmorrhages rarely occur.

CHAPTER VII

FEVERS OF THE DENGUE GROUP

THE relationship between yellow fever, dengue and sandfly fever, has already been discussed at the beginning of Chapter VI, to which reference should be made. Although dengue is closely linked with yellow fever in being transmitted by the same kinds of mosquitoes, not by sandflies as is the case with sandfly fever, it differs from yellow fever and is related to sandfly fever in being rarely fatal ; in having a different geographical distribution ; in never being transmitted from lower animals to man so far as is known, and in producing no immun ty against yellow fever.

Dengue and sandfly fever resemble each other so closely in all their essential clinical features that individual cases often cannot be differentiated on clinical grounds or even by any laboratory tests that are generally available. They can best be studied as belonging to one group for which the most suitable name is the dengue group or the dengue-sandfly fever group.

The treatment and prognosis are exactly the same in both fevers, but preventive measures are on different lines, dealing in one case with mosquitoes, in the other with sandflies. Differential diagnosis is, therefore, of practical importance. In outbreaks it is usually easy to distinguish between dengue and sandfly fever, partly by the prevalence of one or the other vector, and partly by the greater frequency of a rash and a two-phase type of fever curve in dengue than in sandfly fever. In sporadic cases these clues often fail and the physician may have to fall back on the diagnosis of " a fever of the dengue group."

In these sporadic cases, and also in some small outbreaks, the first problem to be solved is whether the fever belongs to the dengue group.

Although not infallible, the following general rules will serve as reliable guides in nearly all cases. They are not based on clinical or laboratory tests because these are seldom available, but chiefly on the exclusion of other diseases which may have similar clinical features.

CLINICAL AND EPIDEMIOLOGICAL FEATURES
(Dengue and Sandfly Fever)

The features common to both diseases are :—

(1) A short, self-limited, fever, with rapid or sudden onset, seldom lasting more than seven days, and with a fever-curve resembling one of the types illustrated in the charts.

(2) No parasites are found in the blood by microscopical examination.

(3) Blood cultures, agglutination reactions, and the usual animal inoculation tests, give negative results.

In 1916 Cleland and Bradley, in Australia, conveyed the disease to four out of seven persons living in a non-infected place by the bites of aëdes mosquitoes which had previously fed on dengue patients. They failed to convey infection to two other persons who were bitten by culex mosquitoes which had fed on infected persons.

In 1924 Siler, Hall and Hitchens carried out very careful experiments in Manila. The chief findings were:—

(1) Dengue was caused in twenty-five out of forty-two persons who were bitten by infected aëdes mosquitoes (*Aëdes ægypti*).

(2) The patient is infective to mosquitoes during the first three days of the fever : but not after the third day.

(3) The mosquitoes did not convey the disease till eleven days after they had fed on an infected person, but when once they became infective they remained so for an indefinite time. (Schule later found that mosquitoes might become infective as early as eight days after biting an infected person.)

(4) Culex mosquitoes failed to infect susceptible persons in the same conditions.

(5) One attack of the disease gave rise to a certain degree of immunity. Of persons reinfected after one to four months, about 50 per cent. were found to be immune ; the others suffered from second attacks which were much milder on the average than the first.

In 1930 Blanc and Caminopetros found that *Aëdes ægypti* might be infected by biting patients as late as the fourth or fifth day of the fever ; and in 1931 Simmons showed that patients were infective on the last day of the incubation period. Still there is general agreement that the first two or three days are the most infective period.

In 1936 Shortt *et al.* reported successful cultivation of the virus, as well as of the virus of sandfly fever, on the chorio-allantoic membranes of developing chick embryos, but the production of the diseases by inoculation of subcultures was not demonstrated.

In 1944 Sabin showed that very young mice were susceptible to inoculation with patients' blood ; in early passages 10–20 per cent. of the mice became infected, in later passages 90 per cent. reacted. In 1948 he described a complement-fixation test with antigen prepared from the brains of infected mice ; he found the reaction positive in monkeys after repeated doses of yellow-fever vaccine, this finding suggests that there is some immunological relationship between dengue and yellow fever.

The above findings include the most important ætiological features of the disease.

Aëdes albopictus has been found to be an effective vector, but *Aëdes ægypti* is the only one of real importance except in a few localities.

Distribution and Epidemiology. This corresponds very closely with the distribution of *Aëdes ægypti*, which is almost universal in the tropics and extensive in sub-tropical countries. The disease is probably more

(8) The epidemiological conditions are suitable for the spread of infection by aëdes mosquitoes or sandflies.

(9) No other form of fever having the above features is known to occur in the area.

Although it is possible that there may be hitherto unrecognised fevers which comply with these nine conditions it may be accepted as a working hypothesis that compliance points strongly to one of the two fevers of the dengue group. On many occasions in the past observers have fallen into the error of assuming that cases of fever which do *not conform to the textbook description of dengue or sandfly* fever must be new diseases. Such mistakes would be avoided if due account were taken of the considerable range of variation that occurs among the fevers of the dengue group. These variations may be due to differences in the strains of the viruses or in the degree of susceptibility of the affected communities. For example, an outbreak of dengue in an area in which the disease is endemic differs greatly from one in a country where no cases have occurred for several years.

The dengue-like Colorado tick fever and Rift Valley fever may closely resemble dengue in their clinical features but they have a strictly limited geographical distribution and there are important differences in the epidemiological conditions in which they occur.

It is also possible that mild forms of yellow fever may occur in areas of Africa and South America and that these may closely resemble dengue both clinically and epidemiologically, but here again knowledge of the distribution of yellow fever and the application of the mouse-protection test are likely to clear up doubts regarding the diagnosis.

DENGUE OR MOSQUITO DENGUE

The name dengue is an old one which is believed to be derived from the Spanish word *denguero*, meaning dandy. The name probably refers to the stiff, dandified gait of some patients who suffer from severe pains in the back and limbs.

Definition. A short fever caused by a special filter-passing virus called the virus of dengue which is transmitted from man to man by aëdes mosquitoes, especially by *Aëdes ægypti*.

Importance. Although seldom fatal, dengue may have serious effects by disabling up to 25 per cent. of a body of troops or civilians for a short time. Also the disease may be very distressing and demoralising to the patients.

History. In 1780 Rush of Philadelphia wrote the first clear account of the disease, which was known locally as " break-bone fever." One of Rush's patients, a young lady, suggested that " break-heart fever " would be a more suitable name.

In 1907 Ashburn and Craig proved that the infection could be conveyed to man by injecting the blood of infected persons, even when the blood had been passed through a Berkefeld filter.

Although the human host is infective to mosquitoes for a very brief period, the infected mosquitoes can transmit infection for the rest of their lives and so are the chief reservoirs of the disease.

The disease may also be maintained by the occurrence of slight unrecognised cases in human beings from whom mosquitoes can acquire infection even when dengue is not known to occur in the locality. From the permanent reservoirs of dengue in the tropics infection is readily carried by human beings to distant places where the disease will promptly break out if vector mosquitoes are present. The question of an animal reservoir has not been properly investigated. Some recent workers claim to have transmitted the disease to monkeys, keeping the virus alive after numerous passages. On the whole, it is unlikely that there is any important animal reservoir of infection other than man, though Lumley's suggestion (1943) of the possible occurrence of " jungle dengue " deserves consideration.

Altitude. Dengue is known to occur up to heights of 4,000 to 6,000 feet near the equator ; in colder countries it is confined to low levels.

Season. The disease may occur at any time of year when active vector mosquitoes abound ; in the sub-tropics it is most common as a rule in autumn. In Palestine, Kligler reports that the disease occurs later in the year than sandfly fever, after all the sandflies have disappeared.

Sex, Age, etc. Dengue is equally common in both sexes. It does not appear to be so common in children, possibly because, like yellow fever, it is so easily overlooked in them.

Race. There is no racial immunity, but the residents in endemic areas naturally suffer less frequently and less severely than newcomers who have not acquired immunity through previous attacks.

Immunity is conferred by an attack, but is often short-lived, and many people have suffered from second attacks within two or three months of the first.

As a rule each succeeding attack is milder than its predecessor ; lasting immunity seems to be gradually built up by a succession of attacks, so that it is unusual for a person to suffer more than three times. Those who are partially immune frequently get very mild attacks which are overlooked, as there may be only a brief rise of temperature with malaise. Such attacks are of importance in building up immunity in the affected persons and also in maintaining the reservoir of the virus: patients suffering from these larval or immunizing attacks may be infective to any vector mosquitoes which happen to bite them.

The occurrence of different strains of the virus complicates the problem of immunity ; later attacks may be caused by different strains, but are more likely to be made possible by the wearing off of the immunity.

Pathology. Reports of the changes found after death are scanty

widely distributed than is usually believed. Dengue is often overlooked when it occurs as sporadic cases, which are common in places where the disease persists in endemic form. Many of the undifferentiated short fevers probably belong to the dengue group. The special prevalence of the disease in coastal, deltaic, and riverine areas is explained by the corresponding distribution of the vector mosquito. The epidemicity is very varied : in tropical areas where the range of temperature is slight and the vector abounds throughout the year, the disease tends to persist as an endemic infection, though it may die down for long periods and then flare up again. Probably the permanent reservoir of the disease is in countries which lie near the equator, where the conditions are favourable for its existence throughout the year. The farther we go from the equator the less favourable are conditions for its continued existence, so that in countries like Greece, dengue may be absent for years ; then if the climatic conditions happen to become suitable, and infection is introduced, the disease spreads like wild-fire among the unsalted population. Places situated at shorter distances from the equator show an intermediate state of affairs. Taking Calcutta, for example, the disease is seen every year in the form of sporadic cases which occur chiefly among newcomers, but from time to time epidemics break out. These are probably explained by the fact that after each epidemic the population as a whole becomes partly immune for the time being though the disease continues to smoulder among the few persons who still remain susceptible. Then a steady increase occurs in the number of susceptibles, through births, immigration, and the wearing off of immunity among those previously attacked, so that the conditions become favourable for rapid spread of the infection.

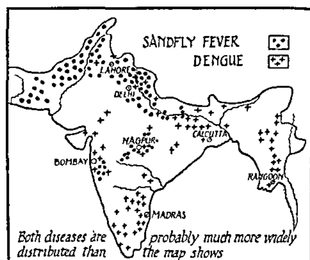


FIG. 28. Map of distribution of dengue and sandfly fever in India.

The factors which influence the distribution of the disease are :—

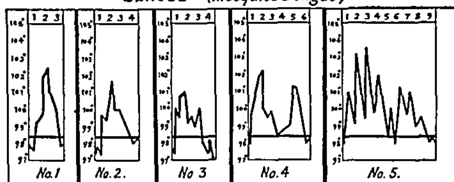
(1) The existence of infection, either in human beings or in mosquitoes which have previously bitten infected human beings.

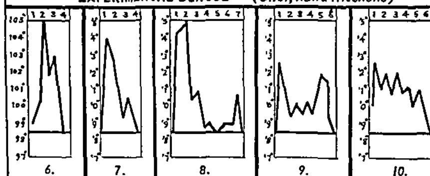
(2) The existence of vector mosquitoes in sufficient numbers.

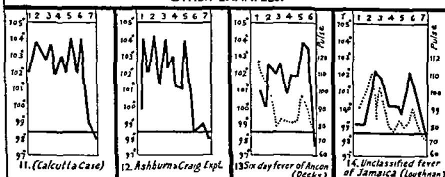
(3) Suitable conditions of temperature and moisture.

(4) The existence of a sufficient number of susceptible persons in the community.

few aberrant forms have been reported in some epidemics, such as cases in which the second phase is longer and more severe than the first ; cases with a third rise of temperature, and cases in which the







Temperature — Plain line
Pulse — Dotted line

Fig. 29. Temperature charts of mosquito dengue.

duration is eight to eleven days. These aberrant forms are so few that any outbreak of fever in which a large proportion of the cases fail to conform with some of the types illustrated in the chart should be suspected of belonging to a different category. This is specially true

and are probably of little importance because death is more likely to be caused by a complication than by the disease itself.

Clinical Features

Almost the only universal manifestation is fever. A study of the temperature charts shows that there is an unbroken series of graduations from a short spell lasting one or two days to a continued fever of five to seven days' duration (*see* Fig. 29, *Charts* 1 *to* 14). The types commonly seen are as follows :—

(1) **The Continued-Fever Type.** This is not common. The temperature remains high during the whole course of the fever, but as a rule there is a " terminal rise " about the fifth or sixth day just before the crisis (*see* Fig. 29, Chart 11).

(2) **The Saddle-back Type.** *In this there is a gradual decline of the* temperature from about the second day, but by the fourth or fifth day, when the temperature is approaching to the normal level, there is a second sharp rise, which is followed in a day or two by the crisis (*see* Fig. 29, Charts 9 and 14).

(3) **The Interrupted-Fever or Two-phase Type.** This differs from the saddle-back type in that the temperature falls completely to normal by the third or fourth day, and rises again on the fourth or fifth day (*see* Fig. 29, Charts 4 and 8).

There is no essential difference between these three types ; all of them show that the fever has a distinct tendency to relapse four to six days after the onset ; the relapse may take on the form of a rapid increase in the fever still present or of a second rise of temperature after a period of freedom from fever ; in either case the periodicity is much the same and appears to be associated with a developmental cycle of the virus. The relapse, when it does occur, is short, being brought to an abrupt end on the sixth or seventh day from the onset *in the great majority of cases, though very exceptionally the fever* may be prolonged till the eighth or even the tenth day. Second relapses have been described, but these are very rare. The normal course of events is for immunity to be established rather suddenly, less than seven full days after the onset.

(4) **The Short-Fever or One-phase Type.** This differs from the two-phase type in that there is a single short spell of fever lasting from one to five days ; evidently immunity has become established before the second phase has had time to begin. In some outbreaks half of the cases are of this type, and when a single sporadic case is seen there is no clinical means of distinguishing the disease from sandfly fever. Usually the simultaneous occurrence of cases of types 2 and 3 makes the diagnosis easy (*see* Fig. 29, Charts 1, 2, 6 and 7).

The " larval " cases with little or no fever may be included in group 4.

Nearly all cases conform to one or other of these types, though a

in the fasciæ, hence they are often periarticular; there is rarely any outward sign of inflammation, but slight redness and swelling of the joints may occur in exceptional cases. The pains usually vary directly with the height of the temperature—they come with the fever, subside when the temperature falls, but return with the secondary rise. Usually they go away for good when the temperature finally falls, but in some epidemics the pains tend to persist in the majority of the persons attacked. The pains are useful diagnostic features when they occur, but it must be remembered that similar pains are common in influenza, relapsing fever, malaria and other fevers.

The Rashes of Dengue. Like the pains, these are very variable. Two kinds of rash are seen :—

(1) The primary rash with pronounced redness of the face, neck, chest, throat, mouth, and eyes; often seen at the onset and during the first day or two.

(2) The secondary, or "true" rash, seen about the fourth to the sixth day; rarely as soon as the second day. It may last for a few hours, but sometimes persists for two or three days. The chief sites are the limbs and trunk; the palms are often affected. The rash is often difficult to detect, especially in dark-skinned patients. Even in white skins it may be obvious in only 10 per cent. of the cases, but in rapidly-spreading epidemics it occurs in 40–95 per cent. of white-skinned patients.

The rash is extremely variable in type, it may be macular, maculo-papular, urticarial, diffusely erythematous, or a combination of two or more of these types. It is often described as measly or scarlatinal. There may be no sharp line of distinction between the primary and the secondary rash.

The rash may be followed by desquamation, which is proportional to the intensity of the rash. Irritation of the palms or a diffuse urticaria sometimes occur; these may persist for several days after the fall of the temperature.

The rash when present is a very useful diagnostic feature, but its absence cannot be regarded as evidence that the disease is not dengue, especially in the case of dark-skinned persons.

Circulatory System. At the onset the pulse is usually rapid in proportion to the temperature, and if the patient has been moving about, a pulse rate of 120 or more is quite common: as the disease progresses the pulse tends to become slow, and may be almost normal, even when the temperature is 102° F. or more. After the fall of the temperature the pulse rate may drop to 50 or 60; in rare cases it may be as slow as 40.

Blood. In uncomplicated cases there is nearly always a progressive leucopenia, beginning about the second day and most pronounced about the fifth day, when the total white-cell count averages 4,000, and in some cases falls to 2,000. The chief reduction is in the mature,

of the duration of the fever ; there is no well-authenticated record of an outbreak of dengue in which a large proportion of the cases had a duration longer than seven days. Even in an individual case, a duration of more than a week is strong evidence against the diagnosis of uncomplicated dengue. In one outbreak described as dengue in which most of the attacks lasted ten to twelve days the disease was flea-borne typhus ; short cases of paratyphoid fever have also been mistaken for dengue.

Other Features of Dengue

The variability of the disease is so great that it would be misleading to describe any one form as being typical.

Incubation Period. The incubation period varies from four to ten days in the experimental cases studied by Siler, Hall and Hitchens. From other evidence it appears to vary from two to fifteen days as extremes, but it is four to eight days in more than 90 per cent. of the cases.

Prodromata. Often there is no warning of the attack, but in about half of the cases there is a feeling of lassitude and general discomfort for a few hours or even for a day or two before the onset. In patients who are attacked in hospital a slight rise in temperature on the day before the onset is often shown on the chart.

Onset. This is usually abrupt ; the patient has been in his usual health, but within half an hour he is quite sure that he is ill, and already his temperature has risen by a degree or two ; within a few hours it may have reached 103° F. or 104° F.

With the rise of temperature there is usually frontal headache, commonly with special localisation of the pain behind the eyeballs. The skin of the face, neck and upper part of the chest is often red ; accompanying this there is injection of the conjunctivæ and congestion of the mouth and throat. Pain in the loins and limbs is usually complained of, chill or shivering occurs in most cases.

On the other hand there may be only headache and fever without any other symptoms, and the onset may not differ in any essential way from that of many other acute fevers.

Pains. Like most of the other features of dengue, these are very variable ; in some outbreaks the pains are so severe in many of the cases as to justify Rush's name " break-bone fever " ; in other outbreaks they are not specially prominent ; some patients do not complain of pain.

Usually there is great physical discomfort and restlessness : the patient may feel compelled to change his position in bed ; having done so, he often finds the new position more uncomfortable than the old.

The pains may be agonising : they are in the loins, the neighbourhood of the joints, the epigastrium, and over or behind the eyeballs. The pains are localised in the tendinous insertions of the muscles and

in 1928 there were 1,240 deaths in 800,000 cases. The risk to life is negligible in otherwise healthy persons, in spite of the apparent severity of the illness.

Diagnosis

Dengue is very easy to detect during a recognised epidemic, but sporadic cases are often missed. Whole outbreaks of dengue have often been regarded as being some new and mysterious malady because the features of the disease have not corresponded with those described in the text-books.

The chief cause of error is that dengue is often assumed to be a disease of which severe pains, a two-phase type of fever and a rash are essential features ; the absence of any or all of these is common in individual cases or even in whole outbreaks, especially when they occur in places in which the disease is endemic. Most of the descriptions of dengue are based on observations of dramatic epidemics among highly susceptible populations. Unfortunately, there is no reliable test on which a diagnosis can be based in any given case, except blood-inoculation experiments on susceptible human beings. As a practical working rule. the features detailed in pp. 130–132 will enable the medical man to place the outbreak in the " Dengue Group," and there will usually be enough evidence to show whether a mosquito or a sandfly is the vector insect.

Diagnostic difficulties sometimes arise in connection with the following diseases :—

Influenza, when uncomplicated, may closely resemble the one-phase type of dengue, but usually the catarrhal signs are much more pronounced in influenza and the epidemiological conditions point to a droplet infection instead of a disease transmitted by mosquitoes.

Sandfly Fever. It may be quite impossible to distinguish between dengue and sandfly fever in certain cases : the point will be discussed in connection with the latter disease.

Yellow Fever. The relationship between yellow fever and dengue has already been discussed.

Measles. The very pronounced catarrhal symptoms, the presence of Koplik's spots, the incidence among children and the spread from person to person by droplet infection are special features of measles.

Scarlet Fever. The appearance of the throat, the early rash, the presence of albuminuria are quite different from what is found in dengue. Scarlet fever is rare in the tropics, and in many places can be ruled out at once.

Rubella. The coryza, early appearance of the macular rash, slight fever and greater glandular enlargement, are distinctive features of rubella.

Small-pox may give rise to difficulty in the pre-eruptive stage, but within four days there will be no room for doubts as to the nature

segmented, polymorphonuclears, which may almost disappear; and although there is an increase in the young, non-segmented forms the total neutrophile count is greatly diminished. The lymphocytes are somewhat diminished in numbers, but after two days they cease to diminish, so that from the fourth day or so they may amount to 50 per cent. or more of the total count. An increase in the total white-cell count nearly always means the presence of a complication, except during the first day or two.

In a very severe epidemic in Beirut in 1945 Hitti *et al.* saw several cases in which there was a tendency to hæmorrhages. Petechiæ often occurred.

Gastro-intestinal. Nausea is common at the onset, there is vomiting in 5–20 per cent. of the cases at this stage. The tongue is usually furred. Anorexia and constipation are usual, there may be a " critical diarrhœa " at the crisis. A " gastric " type of the disease has been described.

Lymphatic Glands. These are sometimes enlarged, especially the cervical, but the enlargement is not great, and in some epidemics the glands have been found to be normal.

Albuminuria. This occurs in some cases, but is seldom pronounced, except in very severe attacks.

Nervous System. Depression and insomnia are common; meningismus is rare. Hysteria, mild delirium and other psychical disturbances sometimes occur.

Respiratory System. Congestion of the pharynx may occur in some cases to such a degree as to suggest influenza.

Dengue in Infants. The disease is not uncommon in infants and young children, but is likely to be overlooked in them unless the rash is pronounced. Epistaxis and convulsions are common in infants.

Complications. Apart from those already mentioned, which are really manifestations of the disease itself, there are remarkably few complications. The coexistence of other diseases may be a troublesome complicating factor. Heat-stroke, to which dengue predisposes, is the probable explanation of most of the cases of hyperplexia that have been reported. In very hot weather the patients need special attention to guard against this risk.

Sequelæ. Depression and loss of appetite may persist for a variable period of days, or even weeks. Grave psychoses are rare. Persistent pains are frequent in some epidemics, not in others. Boils and urticaria may occur. There may be temporary loss of accommodation of the eyes. Orchitis is a rare sequela.

Convalescence. The average period of total disablement for work is about a week to ten days, but partial unfitness sometimes persists much longer.

Prognosis. This is good except in the very young and very old. In large epidemics the fatality rate is 0·2–0·5 per cent. In Greece

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Rubella. The coryza, early appearance of the macular rash, slight fever and greater glandular enlargement, are distinctive features of rubella.

Small-pox may give rise to difficulty in the pre-eruptive stage, but within four days there will be no room for doubts as to the nature

of the disease. Local knowledge of the prevalence of dengue or smallpox at the time will usually facilitate the diagnosis during the early stages of the two diseases.

Early Malignant Tertian Malaria may resemble dengue for a day or two, but proper blood examinations will soon clear up the diagnosis.

Fevers of the Typhus Group may resemble dengue, but these fevers rarely last less than ten days, and the rising-titre Weil-Felix reaction will clear up the diagnosis in most of the doubtful cases.

Typhoid Fever. The continued-fever type of dengue is often diagnosed as typhoid or paratyphoid fever about the sixth day, when the terminal rise of temperature occurs. Blood culture is the only reliable means of early diagnosis of typhoid fever. If this cannot be carried out, and if the course of the fever is compatible with dengue, it is a wise precaution to delay the diagnosis of typhoid till seven clear days have elapsed : in many cases the medical man who finds that the temperature of his patient has gone higher than ever on the fifth or sixth day, sends him to hospital as a case of typhoid, only to be told on the next day that the temperature has come to normal and the patient is convalescent.

Leptospiral Fevers. These, including the unfortunately-named "seven days' fever of Japan," have often been mistaken for dengue. The leucocytosis, and the finding of leptospiræ in experimental animals are distinctive.

Colorado Tick Fever. This cannot be distinguished from dengue on clinical grounds but it is found only in certain areas and is a sporadic zootic, tick-transmitted disease.

Treatment

There is no specific treatment for dengue, and as the disease runs a benign self-limited course, there is no urgent need for drug treatment. For the pains, harmless placebos can be given ; local applications such as liniment of belladonna are useful for those patients who refuse to "grin and bear it." Acetylsalicylic acid may be needed, but it should be withheld when the crisis is due. Quinine aggravates the discomfort. Phenobarbitone (luminal) is useful for persistent insomnia, but the fewer drugs are given the more rapid and satisfactory convalescence will be. A mild laxative is often needed. Ice to suck is useful for nausea ; for vomiting, repeated sips of warm water up to a pint or two are helpful. If the headache is unbearable, lumbar puncture will give relief ; it has been claimed by Le Gac (1948) to be curative.

General Measures. Rest in a comfortable bed, in a cool and airy room, plenty of water to sip, liquid diet if the patient has an appetite, cold sponging if the temperature exceeds 104° F., and reassurance as to the prospect of an early recovery, are the only essentials in most cases. The patient often feels very ill indeed, and it is necessary to be

sympathetic as well as reassuring: he resents being told that his illness is a trifle, when he is painfully conscious of being wretchedly ill.

There is no need to force the patient to eat; a few days' abstinence from solid food does no harm, and the appetite returns all the sooner when the digestive organs have been rested. Plenty of water, with the addition of salt in very hot weather, and glucose solution with orange juice should be given in the acute stage.

During convalescence, liberal diet, fresh air, and a change to a cool climate with cheerful surroundings, are advisable.

Prevention

Very little has been done hitherto in the way of prophylaxis. The rules are exactly the same as for urban yellow fever, viz., destruction of aëdes mosquitoes and the prevention of infection among mosquitoes *by keeping the patients under curtains during the early stages of the illness.* Hospitals in which mosquito nets are not used often become hot-beds of infection. Individual prophylaxis by mosquito curtains *is useful, but aëdes mosquitoes bite by day as well as by night so that* their attentions are difficult to avoid. Spraying the room with a solution of D.D.T. in kerosene and the application of mosquito-repellents such as dibutyl phthalate are useful.

SANDFLY FEVER OR SANDFLY DENGUE

(Phlebotomus Fever, Papataci Fever, Etc.)

Definition. Sandfly fever is a short fever caused by a filter-passing virus called the virus of sandfly fever, which is transmitted from man to man by sandflies, especially *Phlebotomus papatasii.*

The very close relationship between dengue and sandfly fever has already been discussed; the only essential differences between the two diseases are: (1) they are transmitted by different vectors; (2) the viruses are presumably different; (3) a two-phase type of fever is much more frequent in dengue, and correspondingly the average duration of the fever is longer; (4) a secondary rash is common in most outbreaks of dengue, and rare in sandfly fever.

The last two differences are usually so pronounced that it is possible to distinguish outbreaks of the diseases from each other with some confidence on purely clinical grounds, but in sporadic cases differentiation is often impossible unless there is evidence to show which of the two vectors is concerned in transmission.

Various other points of difference have been stated to exist, such as the longer immunity following attacks of sandfly fever and the absence of enlargement of the lymph nodes in that disease, but these features have been found unreliable and the only universal basis of differentiation consists in the vector and the epidemiological conditions associated with the vector.

The diseases presumably do not immunize against each other, but even this point has not been established, and in view of the short-lived immunity that each of the viruses produces against itself evidence

STORY OF TYPICAL ATTACK OF SANDFLY FEVER



1
2
3

A sandfly bites a person suffering from the disease during the 1st or 2nd days of the fever, possibly also before the onset

4
5
6

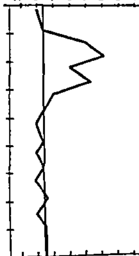
During this period the virus is developing in the sandfly which becomes infective after 7 or 8 days.

7
8



9
1
2
3

The infected sandfly bites a susceptible person and injects the virus into his blood. Incubation period 2-7 days, usually 3·5 days.



4 *Prodromata, malaise, headache.*

5
6
7
8
9
10

Onset sudden with headache, chills, flushed face, injected eyes, pains in back and the limbs etc. as in Dengue. Course of fever just like primary fever of Dengue, relatively slow pulse, pains, restlessness, insomnia, progressive leucopenia.

11
12

Convalescence rapid, but patient often feels depressed for several days.

FIG. 30. Story of a typical attack of sandfly fever.

is not easy to obtain. It ought to be easy to determine whether the virus of dengue can be transmitted by the sandfly and whether the virus of sandfly fever can be transmitted by *Aëdes œgypti*, but this crucial experiment has not yet been carried out.

Anyhow, from the clinical point of view the description of dengue

is equally applicable to sandfly fever if it is borne in mind that a second rise in temperature and a secondary rash are far more frequent in dengue.

The epidemiological and preventive aspects of the two diseases are quite different.

History. The disease was described by Pym in 1804, and was well known by British medical officers in Mediterranean stations since that time under such names as febricula, climatic fever, or P.U.O. (pyrexia of unknown origin).

In 1905 Taussig described the disease as occurring on the Adriatic coast and accused sandflies of being the vectors.

In 1907 Doerr, Franz and Taussig investigated the disease and reached the following conclusions : (1) The virus is present in the blood during the first day of the fever, not at later stages ; (2) the virus is filterable through a Berkefeld filter ; (3) the virus is conveyed by *Phlebotomus papatasii*.

Sandflies were fed on patients during the first day of their illness, and after being kept for several days were allowed to bite volunteers, who, in due course, suffered from typical attacks.

In 1908 Birt confirmed the work of Doerr, and found that the sandfly did not become capable of infecting susceptible volunteers till at least seven days after biting an infected person.

In 1934 H. E. Shortt in India found that blood taken from patients on the second day of the fever was still infective. He also found that *Macacus rhesus* monkeys appeared to be susceptible, but had mild attacks.

Distribution. It is chiefly a sub-tropical disease affecting places which have a hot season and abundant sandflies. Unfortunately, the descriptions of outbreaks often leave room for doubt whether the disease was dengue or sandfly fever, so that some epidemics recorded as being "sandfly fever" in tropical localities like Ceylon, Aden, Hong Kong, etc., may really have been dengue.

The known distribution of the disease is much more restricted than that of dengue. The chief foci of infection lie in the countries of South-Eastern Europe, North Africa, the Middle East, including India and the countries of southern Asia lying to the west of India. Outbreaks have been reported from Panama, Brazil and Argentina in the American Continent.

In countries that have a cold season the disease occurs only in hot weather when conditions favour the prevalence and activity of the vector insects.

It may occur up to a height of 7,000 feet in the Himalayas, but in Europe it is rare above 1,500 feet.

Like dengue, it may occur in sharp explosive epidemics in which 90 per cent. of the population are affected ; but in many places it is endemic, attacking chiefly newcomers from places where the disease

does not occur. It varies greatly in severity in different outbreaks and in different localities.

Immunity. This is usually stated to be more lasting than in dengue, but recent reports of outbreaks show that second attacks after short intervals are frequent, and that third attacks may occur during one season.

Ætiology. This has been dealt with in connection with the history of the disease ; it follows the same lines as dengue, but there are differ-

SAND-FLY FEVER

(or Sand-fly Dengue)

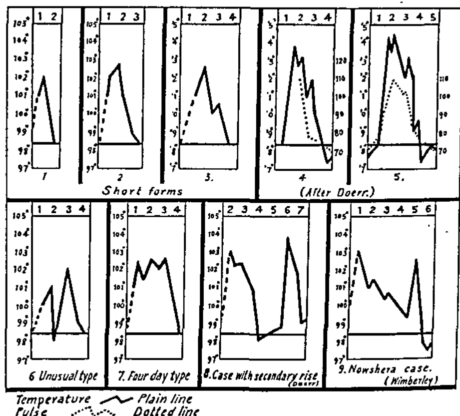


Fig. 31. Temperature charts of sandfly fever.

ences in detail which are dealt with in the table below. The sandflies breed chiefly in crevices of walls, between planks, under the bark of trees, in rubbish, but perhaps the most important breeding grounds are the moist stony beds of water-courses in which water has ceased to flow for the time being. Sandflies are uncommon when the houses and surroundings are tidy. The virus may perhaps be conveyed from an infected sandfly to its offspring.

Symptoms. The symptoms are exactly similar to those of the short-fever forms of dengue ; the sudden onset, often with shivering, the redness of the face, neck and conjunctivæ, the pains, gastro-intestinal

symptoms, bradycardia and leucopenia all occur with about the same degree of frequency in the two diseases.

DIFFERENCES BETWEEN DENGUE AND SANDFLY FEVER

	Dengue	Sandfly fever
Suggested name	Mosquito dengue.	Sandfly dengue.
Most infective period	First three days.	First two days.
Chief vector	*Aëdes ægypti.*	*Phlebotomus papatasii.*
Climatic distribution	Chiefly tropical. May also be sub-tropical.	Chiefly sub-tropical. May also be tropical.
Symptoms	Secondary rise of temperature in 25–80 per cent. Secondary rash in 10–95 per cent. in various outbreaks.	Secondary rise of temperature not common. Secondary rash rare.

Secondary rises of temperature and late rashes are exceptional, but undoubtedly they sometimes occur. For the differential diagnosis from other diseases than dengue, see the preceding account of dengue.

The prognosis, complications and treatment of sandfly fever do not differ in any important respect from those of dengue.

Prevention. This consists in destruction of the sandfly, preventing it from biting by using a fine-mesh net, and by the repellents used in the prevention of malaria. Ordinary mosquito nets sprayed with a D.D.T. solution have been found effective in keeping out sandflies and are much more comfortable than the fine-mesh nets. In hospitals and camps the rooms or tents should be sprayed at least once daily, and all infected patients should be kept throughout the twenty-four hours under fine nets. The other patients should also be kept under nets as far as possible. Hospitals may become hotbeds of infection ; their staff should take special precautions against infection because temporary disablement of the personnel may cause serious dislocation of the work.

The breeding-places of sandflies are not easy to find ; even experts may encounter difficulties. A determined effort should be made to control these insects ; they make life a burden when they are plentiful, and convey a very unpleasant disease. Tidiness of the immediate surroundings of houses or tents is essential. Spraying the inside and immediate surroundings of the house once a week with D.D.T. solution is likely to be of value.

The upper stories of houses are much less infested by sandflies than the lower.

OTHER FEVERS OF THE DENGUE GROUP

As has already been stated, many outbreaks of short benign fevers which were really varieties of dengue or sandfly fever have been wrongly

described as "new diseases" and have been given misleading names. There are, however, two other benign short fevers caused by filterable viruses, called Colorado tick fever and Rift Valley fever, which in spite of their close clinical resemblance to dengue and sandfly fever respectively have been shown to be quite distinct diseases. They can *provisionally be classified as fevers of the dengue group*, and although they are not known to occur outside their own limited geographical areas, and so are of only local importance, they deserve to be briefly described as examples which suggest that other "dengue-like" fevers may still await identification.

Colorado Tick Fever

Definition. A benign zootic short fever caused by a special filter-passing virus transmitted from wild rodents to man by ticks, chiefly by *Dermacentor andersoni*. Clinically the disease closely resembles dengue and it may be provisionally classed as "tick dengue."

History. It was described by Becker in Colorado in 1930 and has been studied by Topping *et al.* in 1940 and by several workers since that time, especially by Florio.

Distribution. The disease is known to occur in Colorado and several other States in the south and west of the U.S.A. The virus has been isolated from ticks in New York State, but no human cases have been detected in that region.

Ætiology and Epidemiology. The virus has been transmitted experimentally from hamster to hamster by the tick *D. andersoni*, and to man by yolk-sac cultures. Very young mice are susceptible to inoculation. The virus is immunologically distinct from the virus of dengue. The disease occurs sporadically in man, chiefly in the months of May, June and July.

Clinical Features. These are exactly like those of dengue except for the absence of a rash. The fever curve is of the two-phase type in most of the cases.

Rift Valley Fever

Definition. A benign zootic short fever caused by a special filter-passing virus transmitted to man from infected cattle or sheep among which it occurs as a highly fatal infection called enzootic hepatitis.

The disease takes its name from the Rift Valley in Kenya where it was discovered by Daubney *et al.* in 1931. By a mouse-protection test like that used in yellow fever evidence has been found of the probable occurrence of the disease in the south of the Anglo-Egyptian Sudan, in Uganda and in French Equatorial Africa.

Many lower animals are highly susceptible to inoculation with the virus which often causes necrosis of the liver in them.

Laboratory workers who study the virus are often attacked ; this

circumstance and the special association of the disease with work among cattle and sheep suggest that infection may be by direct contact such as happens in Q fever though the usual view is that various kinds of mosquitoes transmit the infection. The virus is quite distinct from that of dengue and sandfly fever but the disease in man closely resembles the latter disease in its clinical aspects.

J. W. D. MEGAW

CHAPTER VIII

THE RICKETTSIAL FEVERS

Seven fevers are known to be caused by rickettsiæ ; they are : (1) louse-borne typhus ; (2) flea-borne typhus ; (3) tick-borne typhus ; (4) mite-borne typhus ; (5) trench fever ; (6) Q fever ; and (7) rickettsialpox.

The **Rickettsiæ** are elusive microbes which were first detected in 1909 by Ricketts, who found them in animals inoculated with Rocky Mountain spotted fever ; soon they were found by Prowazek in his studies of louse-borne typhus. They were fully investigated by da Rocha Lima who, in 1916, called the rickettsia of louse-borne typhus *Rickettsia prowazeki* in honour of Ricketts and Prowazek, both of whom died of infection contracted in the course of their research.

It was not till several years later that the rickettsiæ were generally accepted as being pathogenic microbes : the reason for this delay in their recognition was that they are only just visible as minute dots, rods, or threads when examined in stained films with the most powerful ordinary microscopes so that they could hardly be distinguished from granular debris and filaments such as are often seen in smears made from healthy tissues and body fluids.

Another difficulty was due to their being incapable of cultivation in ordinary laboratory media. They are about 3 to 5 μ in diameter and some of them are filter-passing. They can be stained with Giemsa's or Leishman's stains.

Examined with electron microscopes, they are found to resemble bacteria in their structure and they are now regarded as being more closely related to bacteria than to filter-passing viruses, though they are like the latter in growing inside or in close association with the cells of infected animals and in refusing to multiply in media which do not contain living cells. They are usually cultivated in the yolk sacs of living embryo chicks or in tissue cultures.

Their isolation and identification is difficult and is seldom undertaken except by highly skilled experts in special laboratories ; the methods employed include the intraperitoneal inoculation of susceptible animals such as mice and guineapigs with the blood of patients ; it is often necessary to make further passages of blood or tissue suspensions from the inoculated animals to other animals or to the yolk sacs of developing chicks.

A differential diagnosis of the fevers is made by complement-fixation or rickettsia-agglutination tests of the sera of patients or of inoculated animals ; but even when facilities for these tests are available the results are seldom known till the end of the second week of the

illness. In view of the discovery of effective drugs for the treatment of these diseases early diagnosis has become very important so that medical men must endeavour to recognise them within the first few days by their clinical and epidemiological features.

All the specific rickettsiæ which cause rickettsial fevers have one feature in common ; each of them can live and multiply in two widely different kinds of host, one of which is a vertebrate animal and the other an arthropod which transmits infection from one vertebrate to another.

A remarkable feature of the rickettsial fevers is that, with the exception of Q fever, each of them is transmitted to man by one particular kind of arthropod, and so far as is known each disease would soon cease to occur in man if the arthropod concerned were eliminated.

The vector arthropods associated with transmission to man are : (1) **Human Lice** which transmit louse typhus and trench fever from man to man ; (2) **Rat Fleas,** transmit flea typhus from rat to man ; (3) various **Ticks,** transmit tick typhus from lower vertebrates to man ; (4) certain **Mites** transmit mite typhus and rickettsialpox from rodents to man.

The manner of transmission of Q fever is not fully known ; it is probably for the most part by contact with lower vertebrates, but among these it seems likely that the continued existence of the disease depends on transmission by ticks, so that these arthropods are probably essential for the persistence of the human disease.

The vertebrates from which arthropods transmit infection to man are known as the vertebrate reservoirs of infection.

It should be noted that the arthropods do not necessarily transmit infection by their bites ; a common mode of transmission is by depositing infected fæces on the skin of the host and the entry of infection through abrasions made by scratching. There are other ways in which rickettsiæ are conveyed from the arthropod to the host, but irrespective of the mechanism employed the arthropod concerned is rightly called the vector.

THE DEMIC AND ZOOTIC RICKETTSIAL FEVERS

The rickettsial fevers fall into two groups which differ sharply from each other in certain important epidemiological respects. Suitable descriptive names for these groups are **Demic** and **Zootic.** Demic diseases can be defined as purely human diseases which depend for their continued existence on the transmission of infection from man to man. Zootic diseases primarily affect lower vertebrates and depend for their continued existence on transmission of infection among these lower animals ; the infection of human beings is a secondary incident ; man to man transmission is rare, and when it occurs the infection soon dies out.

The demic rickettsial fevers are louse-borne typhus and trench

fever, both of which are transmitted from man to man by human lice. All the other rickettsial fevers are zootic ; they are : (1) flea-borne typhus, which is transmitted from rat to rat by rat fleas and rat lice ; it is transmitted from rat to man by the rat flea ; (2) Tick-borne typhus, transmitted among lower vertebrates by certain ticks and from lower vertebrates to man by ticks ; (3) Mite-borne typhus, transmitted chiefly among rats by mites, and from rat to man by mites ; (4) Rickettsialpox, transmitted among house-mice by mites and from house-mouse to man by mites. The modes of transmission of Q fever among lower vertebrates and from lower vertebrates to human beings are not fully known ; tick transmission among lower animals may serve to maintain the virulence of the infection among them, but transmission from lower animals to man is chiefly by contact and seldom by ticks. Transmission from man to man by contact occasionally occurs but has never been known to maintain the disease among human beings for more than one or two passages so that Q fever is essentially a zootic disease.

The distinction between demic and zootic rickettsial fevers is of great practical importance ; preventive measures against the demic diseases are directed to the infected persons and human lice ; in the case of the zootic diseases, apart from Q fever, the patient is rarely a source of infection to contacts, so that prevention is by destroying or avoiding the arthropod vectors and their lower-animal hosts in the places where they occur.

The distinction is also important in diagnosis ; useful clues are often provided by such points as the presence or absence of louse infestation, a history of recent bites by the vector arthropods of the zootic diseases or a history of exposure to risk of bites by these arthropods.

The name demic is more suitable than the commonly employed name epidemic because the latter is generally accepted as indicating a high rate of occurrence or a large outbreak of an infectious disease among human beings irrespective of the source of infection ; so, for example, we speak of an epidemic of mite-borne typhus or of bubonic plague though these diseases are transmitted to man from lower animals. Another objection is that the diseases transmitted from man to man often occur in endemic as well as in epidemic form. So also the name zootic is preferable to such names as non-epidemic, epizootic or enzootic which indicate rates of incidence of diseases among human beings or animals.

In view of the importance of the distinction between primarily human and primarily lower-vertebrate diseases there is a real need for suitable and unambiguous descriptive names for the two epidemiological types.

Some of the chief features of the rickettsial fevers are shown in the table.

THE RICKETTSIAL FEVERS

	The typhus-group fevers				Other rickettsial fevers		
	Demic (human)	Zootic (primarily of lower vertebrates)			Demic (human)	Zootic (primarily of lower vertebrates)	
Names	Louse typhus, exanthematic typhus.	Flea typhus, murine typhus, endemic typhus.	Tick typhus, Rocky mountain spotted fever, boutonneuse fever.	Mite typhus, scrub typhus, tsutsugamushi disease.	Trench fever, Volhynian fever, five-day fever.	Q fever.	Rickettsialpox.
Rickettsia	*R. prowazeki.*	*R. mooseri.*	*R. rickettsi* and *R. rickettsi* var. *conori.*	*R. tsutsugamushi* (*R. orientalis*).	*R. quintana* (*R. volhynica*).	*R. burneti.*	*R. akari.*
Chief vectors	Human lice.	Rat-fleas.	Various ticks.	Mites.	Human lice.	Ticks * (among lower animals).	Mites.
Chief vertebrate reservoirs	Man.	Rats.	Various rodents, dogs.	Rats, voles.	Man.	Many lower animals.	Mice.
Geographic distribution.	Cosmopolitan, rare in regions of constant heat.	Foci in most tropical and sub-tropical climates.	Foci in every continent.	Oriental. India, Ceylon, the Far East, Japan, N. Australia.	Poland, N. Africa.	Probably world-wide.	New York State.
Weil-Felix reaction :—							
Proteus OX19	++ to ++++	++ to +++	— to +++	— to +	—	—	—
Proteus OX2	— to ++	— to +	— to +++	— to ±	—	—	—
Proteus OXK	— to ±	— to ±	— to +	++ to +++	—	—	—
Primary local lesion.	None.	None.	Rare except in boutonneuse fever.	Common in some foci, rare in others.	None.	None.	Always present.
Fatality rate per cent.	3 to 40	0 to 5	2 to 80	2 to 50	0 to 1	0 to 3	0
Average ditto	15	2	10	10	½	1	0

* Ticks are probably essential for maintenance of infection among lower vertebrates, but seldom transmit infection to man.

THE FEVERS OF THE TYPHUS GROUP

The four most important rickettsial fevers have so many clinical features in common that it is often impossible to differentiate them without special methods of investigation.

Their study is greatly simplified by regarding them as belonging to one group for which the most suitable name is the typhus group. The most striking respect in which they differ from one another is that each is transmitted to man by a special kind of vector so that they are best classified and named in accordance with the vector as (1) louse typhus, (2) flea typhus, (3) tick typhus, and (4) mite typhus.

The inclusion of the typhus-like fevers in a typhus group was tentatively suggested in 1917 by the present writer, who later, in 1921, proposed that the fevers of the group known at that time should provisionally be classified and named in terms of the vectors as louse typhus, tick typhus and mite typhus. When flea-borne typhus was later discovered it fitted automatically into the classification as flea typhus.

The purpose of the classification was to obviate the confusion already resulting from the coining of new and misleading names for outbreaks in different parts of the world of fevers which could rightly be included in the typhus group. The need for a simple system of the kind has become obvious ; at least fifty different names have been proposed for tick-borne, flea-borne and mite-borne fevers, all of which could rightly have been called by one of the three names just mentioned, with the addition when necessary of a sub-title to indicate a special variety of the fever.

An alternative classification was proposed ; this was based on the type of Weil-Felix reaction observed among patients suffering from the fevers ; it was believed that the different types of reaction corresponded to differences in the antigenic structure of the causative rickettsiæ. It was therefore suggested that the fevers should be classed as typhus of the *Proteus OX*19, *Proteus OXK*, and indeterminate types. This classification broke down because the *Proteus OX*19 type of response occurs uniformly in louse-borne and flea-borne typhus and also in many cases of tick-borne typhus. The *Proteus OXK* type is the only one that corresponds consistently with a single clinical and epidemiological form of typhus, viz., mite-borne typhus.

The situation has been clarified by the employment of the modern complement-fixation test which has been found by Bengtson, Plotz and many other workers to give results which correspond closely with the classification according to the vectors. With rickettsia-agglutination and cross-immunity tests the same correspondence is found to occur, so it is now generally agreed that each vector transmits one, and only one, type of typhus fever.

There are differences of opinion with regard to the number of

rickettsial fevers that should be included in the typhus group; some observers believe that the louse-borne and flea-borne types are the only ones entitled to the name typhus; others would include all the rickettsial fevers. Customary usage and practical convenience are in favour of admitting the four fevers already mentioned, all of them are commonly called typhus. On the other hand trench fever, Q fever and rickettsialpox differ from the typhus fevers in their clinical features and also in giving negative reactions with all the proteus bacilli used in the Weil-Felix test. So it appears that the four typhus fevers have a related antigen in common and that none of the other three fevers possesses this type of antigen.

LOUSE TYPHUS

(*Synonyms:* Louse-borne typhus, typhus fever, typhus exanthematicus, historic typhus, classical typhus, epidemic typhus.)

In German the name typhus means typhoid (*Typhus abdominalis*).

Definition. A demic fever caused by *Rickettsia prowazeki*, which is transmitted from man to man by human lice. The disease is the only form of demic typhus, it often occurs in epidemics, but may be endemic or sporadic.

Historical. The disease is of great antiquity; the first clear account was written by Fracastorius who described it under the name "febris pestilens" about 1530. Since that time there have been many graphic descriptions of epidemics in European countries; most of these epidemics were in armies, prisons, ships, and law courts. The general population of affected countries were attacked chiefly in times of famine. Some of the descriptions were confused because relapsing fever and typhoid fever often occurred at the same time and were regarded as the same disease. The name typhus seems to have been used for the first time by Sauvages in 1760, but many different names were given to the disease.

In 1837 Gerhard showed that typhoid was a different disease.

In 1843 Henderson differentiated relapsing fever from typhus.

In 1909 C. Nicolle, Comte and Conseil showed that the disease could be transmitted by lice.

In 1910 Ricketts and Wilder found that infected lice contained certain bodies which were later described accurately by da Rocha Lima, who called them *Rickettsia prowazeki*. These are now universally recognised as the causal organisms of the disease.

In 1910 W. J. Wilson found that certain organisms of the coli group, which had been isolated from typhus patients, were agglutinated by the serum of persons suffering from the disease; he carefully avoided any suggestion that the serum response indicated that the bacteria were the causal organisms of typhus fever.

In 1914 Weil and Felix, using strains of *Proteus X*, which had also

been isolated from typhus patients, described the agglutination reaction which is now called by their names. This should properly be called the Wilson-Weil-Felix reaction.

In 1916 da Rocha Lima called the causal agent *Rickettsia prowazeki.*

Geographical Distribution. The disease has a cosmopolitan distribution like that of relapsing fever except that it is not common in tropical countries except at altitudes of 3,000 feet or over. In places with constantly hot weather the disease is rare. The distribution of typhus fever became much more restricted by the end of the nineteenth century; it had practically disappeared from the U.S.A. and the countries of Western Europe where louse-infestation had been greatly reduced.

During and after the 1914–18 war great epidemics occurred in Eastern and South-Eastern Europe; in Russia there were more than ten million cases in 1919–20. With a return to peacetime conditions the disease again subsided, but it persisted in endemic form with occasional epidemics in Eastern Europe, North Africa, South Africa, North-East Asia, Persia, Mexico, Peru, Chile, and other countries.

During the second world war there was again a great increase in the prevalence of the disease in Europe, the Middle East and Africa, but by 1949 the number of cases in the affected countries had fallen to a remarkable degree; for example, in Egypt there were 40,000 cases in 1943 and only 186 in 1949.

Seasonal Prevalence. The greatest prevalence is usually in the cold season and the early part of the hot season. After a spell of continued hot weather the disease may almost cease to occur, but with the return of cold weather it commonly increases and reaches its maximum prevalence by the end of the winter. Among overcrowded and louse-infested communities infection may persist till the whole population has become immune through attacks of the disease.

Age and Sex Distribution. People of both sexes and of all ages are susceptible. In very young children the attacks are often so mild as to escape detection. In endemic areas the disease often occurs chiefly among children; the adult population may be largely immune because of previous attacks.

Ætiology. The organism, *Rickettsia prowazeki*, is present in the blood and organs of patients during the acute stage of the illness and sometimes also during early convalescence, it is conveyed from man to man by human lice, especially the body louse (*Pediculus corporis*).

When the louse bites an infected person the rickettsiæ swallowed with the blood multiply rapidly in the gut cells of the insect and escape into the fæces; within a week to ten days the louse becomes capable of infecting any susceptible person with whom it comes in contact. It does not infect directly by biting, because the rickettsiæ do not enter its salivary glands; what happens is that the infected fæces are

deposited on the skin and enter the body through the puncture made by the louse or through abrasions made by scratching. Infected lice are persistent wanderers and a single insect is capable of infecting any person whom it visits. Rickettsiæ can survive for months or even years in the dried fæces of infected lice and there is evidence suggesting that persons who handle the clothing of patients are liable to be infected by inhaling dust coming from the garments after they had been stored for long periods. This source of infection is of little importance during epidemics, but it may be responsible for some of the mysterious fresh attacks in places that have been free from the disease for a long time.

Infection may also be maintained by the occurrence of undetected attacks in children, who often get the disease in a very mild form, or in persons who are partly immune because of previous attacks.

Infection is believed to persist indefinitely in some persons after attacks so that there may be a recrudescence of the disease, usually in a mild form, years after the original attack. This is probably the explanation of Brill's disease.

The rickettsial agent, *Rickettsia prowazeki*, is very like the rickettsiæ of the other rickettsial fevers already described (*see* p. 150).

Monkeys are susceptible to inoculation but guineapigs are usually employed for the isolation of the rickettsiæ by intraperitoneal inoculation of the blood of patients. The guineapigs usually develop a mild attack of fever, and when male animals are employed they seldom have the scrotal swelling such as occurs after inoculation with the blood of patients suffering from flea-borne typhus.

Immunity. This is usually complete for a few years after an attack, but it gradually diminishes so that second attacks, which tend to be mild, may occur.

Pathology. The rickettsiæ multiply chiefly in the endothelial cells of the small blood vessels. These cells become swollen and proliferated. The rickettsiæ and their toxins penetrate the walls of the vessels and cause *small nodular infiltrations* of mononuclear and polynuclear cells on the outside of the vessels. These infiltrations are called " typhus nodules " ; they are best seen in microscopic sections of the brain and skin. The mechanical damage to the vessels is the essential lesion of the disease, it is responsible for obstruction of the lumen of the arterioles and so of the blood supply of the brain ; it also causes hæmorrhages into the skin in the form of petechiæ. The symptoms associated with the nervous and cardiovascular systems are believed to be due largely to the vascular lesions, though the toxins produced by the rickettsiæ also play an important part.

The naked-eye changes seen after death may be slight ; the petechial rash is often visible, the spleen is enlarged ; there may be hæmorrhages, usually petechial, in the pons, medulla oblongata, serous membranes and other parts of the body.

Clinical Features. The disease varies greatly in severity. Mild

attacks of fever lasting a few days, and without special symptoms, may occur in children and in partly-immune persons ; these are very important because they are unlikely to be recognised, so that infection may be established in a community before suspicion of its existence is aroused.

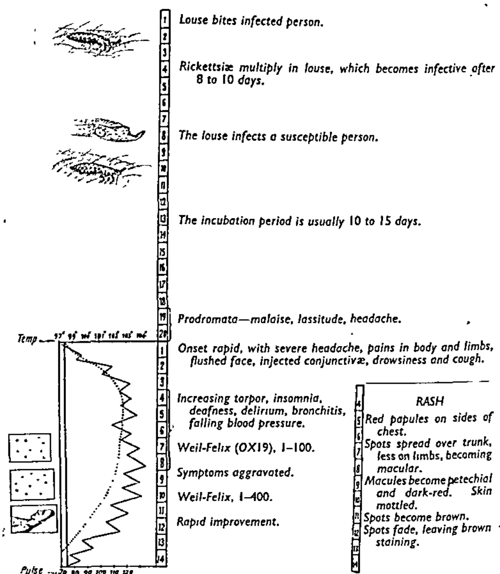


FIG. 32. Story of an attack of louse typhus.

Weil-Felix tests should be carried out in all cases of unexplained fever in places where there is the slightest possibility of the occurrence of the disease.

At the other end of the scale are the fulminating attacks with death within the first few days ; these nearly always occur in severe epidemics among impoverished communities.

The following description refers to rather severe attacks such as

are usual in epidemics. Mild isolated attacks are usually missed, they can hardly be recognised unless special tests are made.

Incubation Period. This is rarely less than eight days; it is usually ten to fifteen days, but may be as long as twenty days or even more. The longer the incubation period the milder is the attack, as a rule.

Onset. This is usually rapid, with a chilly feeling, shivering, or even rigor (60–80 per cent.).[1] There is nearly always a frontal headache (90 per cent.); pains in the back and limbs are usual: vomiting is common (25–50 per cent.); when severe it is accompanied by epigastric pain. The temperature rises rapidly; the rise may be step-like but it is steeper than in typhoid: the onset is less sudden than that of influenza or dengue.

Early Symptoms. Quite early in the course of the fever the face is flushed, the expression dull, the conjunctivæ congested and the eyelids swollen. Drowsiness is almost universal at the onset, but it may soon be replaced by delirium, which is sometimes the first obvious symptom in severe cases. Inability to protrude the tongue is described as occurring early in the course of the disease in many cases.

Symptoms at the Height of the Disease. Insomnia is common (60 per cent.). The temperature usually reaches its maximum within two or three days, and remains high for several days with morning remissions of one to three degrees.

The patient often shows pronounced nervous symptoms by the third or fourth day, whereas in typhoid fever these appear only after ten days to a fortnight; the "typhoid state" is often well-developed within the first four to seven days in severe cases of typhus fever.

The usual features of the middle period of the fever are an aggravation of the nervous symptoms, partial deafness, constipation, a peculiar musty or mousy odour, the spleen is slightly enlarged, the tongue is coated, but may be dry or moist. The throat is red (30 per cent.); there is usually a moderate degree of bronchitis. Constipation is usual.

The Rash. On the fourth or fifth day rose-red papules begin to appear on the sides of the chest, spreading rapidly to the abdomen, back and limbs. The spots are abundant. At first they fade on pressure. Within a day or two they enlarge and become dark-red, then brown, macules, which cease to disappear on pressure. The spots are usually 2–7 mm. in diameter. In severe cases the spots have a hæmorrhagic point in the centre surrounded by a brownish mottling. By the tenth day the spots are dark-brown, and a day or two later they disappear, but a brown staining at the site of the spots may be obvious for several days, sometimes even for two or three weeks after the temperature has fallen.

[1] The figures given in brackets refer only to certain outbreaks; in some epidemics the incidence of the special features is quite different.

The rash is often absent or faint in dark-skinned patients. The spots are sometimes few and inconspicuous, sometimes profuse and widespread ; they are usually macular or petechial but may be maculo-

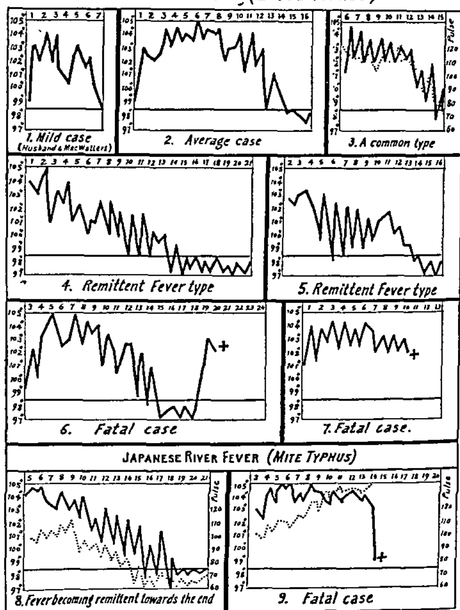


FIG. 33. Temperature charts of louse typhus and of mite typhus (Japanese river fever).

papular ; in severe cases there may be large purpuric patches. The sides of the chest and back are the favourite sites of the eruption ; the trunk as a whole is almost invariably affected : the eruption extends to the arms and legs (70–80 per cent.) ; the face is rarely affected (4 per cent.), the palms and soles still less frequently (1–1½ per

cent.) ; in some outbreaks spots on the palms and soles are said to be relatively common.

The Fever Curve. Some of the types of fever curve are shown in the chart. The temperature rises rapidly or abruptly, sometimes there is a step-like rise as in typhoid, but steeper. The maximum is reached by the third or fourth day ; then there is usually a period of continued fever lasting eight to eleven days. If the temperature is taken every two hours it will often be found that there is a difference of 2 or 3 degrees between the maximum and minimum of each day. Towards the end of the fever the remissions become greater, and the temperature usually becomes normal between the twelfth and sixteenth days. In mild attacks the duration may be as short as nine days ; prolongation beyond the seventeenth day is unusual except in fatal or complicated cases. (*See* Fig. 33, Charts 1 to 7.)

The temperature falls by rapid lysis, less often by crisis. A temporary fall to normal or a deep remission is not uncommon from the second to the fourth day of the fever.

Circulatory System. The pulse rate often rises before the onset of the fever ; it is rapid during the first few days, then it becomes slow in proportion to the temperature in many cases ; there may even be bradycardia.

The systolic blood pressure is usually low ; failure of the heart and circulation are not uncommon towards the end of the fever and in the early stages of convalescence.

A moderate degree of leucocytosis is usual ; in very severe attacks counts of 25,000 or more may be found, especially when there are respiratory complications.. In mild cases leucopenia is not uncommon.

The red blood cells and hæmoglobin may show apparent increases, even up to 25 per cent. above normal, but this is due to dehydration ; there is really a diminution in the total red blood corpuscles and hæmoglobin of the body.

Spleen. This is palpably enlarged in about 25 per cent. of the cases.

Gastro-intestinal. The tongue is coated and is often dry. There may be sordes on the lips and teeth. Constipation is usual, but occasionally diarrhœa with blood-stained stools occurs in severe cases. Diarrhœa with the fall of temperature is not infrequent ; this is described as " critical diarrhœa." Tympanites is not common.

Urine. Febrile albuminuria is common ; nephritis is unusual. Red blood corpuscles may be found in the urine, usually in small numbers, but they may be numerous.

Nervous Symptoms. The brunt of the intoxication falls on the nervous system : frontal headache at the onset is almost invariable. There is dullness, apathy or drowsiness at the onset, later on delirium is usual ; insomnia and partial deafness are common. During convalescence there may be forgetfulness, melancholia, or even mania ; the partial deafness may persist for weeks or months.

Lungs. Bronchitis of varying degree is usual. Broncho-pneumonia is one of the severe manifestations and is often the apparent cause of death ; it occurs in 10–20 per cent. of the cases.

Other Features. Thrombosis of the femoral vein is not uncommon. Gangrene from arterial thrombosis occurs in 1–5 per cent. of the cases ; there may be loss of the toes, or even of one or both feet. There is a special tendency to streptococcal infections in various parts of the body ; otitis may occur in 10 per cent. of severe cases, erysipelas in 3 per cent. and parotitis in 2–4 per cent. Bed-sores are common when the nursing arrangements are defective. In outbreaks affecting well-nourished persons complications are exceptional among young patients.

Prognosis

Louse typhus is not so fatal a disease as it is commonly believed to be ; although virulent epidemics in starved communities may have fatality rates of more than 50 per cent., the average rate is probably less than 15 per cent., and in outbreaks in well-nourished communities it is often less than 10 per cent.

The prognosis depends to a remarkable degree on the age of the patients. Taking 15 per cent. as the average fatality rate, the percentage of deaths at different ages is approximately as follows :—

Age	Fatality Rate	Age	Fatality Rate
2 . .	7 per cent.	40 . .	30 per cent.
10 . .	3 ,,	50 . .	45 ,,
20 . .	6 ,,	60 . .	55 ,,
30 . .	14 ,,		

In severe epidemics few persons over fifty years of age survive.

Most of the deaths occur between the ninth and the sixteenth day of the illness, but in fulminating attacks the patient may die as early as the third day, and in cases with complications death may be delayed till the twentieth day or later.

Treatment with the new antibiotics, chloromycetin (chloramphenicol) and aureomycin, can be expected to cause a great reduction in the fatality rate of the disease (*see* p. 165).

The severity of the nervous symptoms early in the attack is a reliable guide to the prognosis.

Unfavourable features are : early onset of severe neurological symptoms ; hæmorrhagic rash or other hæmorrhages ; broncho-pneumonia ; thrombosis of the veins ; or a leucocytosis in excess of 20,000.

Diagnosis

In sporadic cases diagnosis may be quite impossible till the rash appears ; if this is absent the disease will be wrongly diagnosed unless the physician happens to suspect typhus, in which case he will have to depend on the Weil-Felix test. Till now this has been the only diagnostic

test that has been available to the physician, and in spite of its not being a truly specific reaction it is very helpful in most cases.

A reliable suspension of *Proteus OX*19 is used and the test is carried out in the same way as the Widal reaction. Important points to be noted are : (1) the strength of the reaction is very variable ; usually it becomes positive in high dilutions such as 1–400 or more, but in some cases it is weakly positive or even negative. (2) The reaction usually begins to be positive towards the end of the first week, but occasionally it is delayed till later ; exceptionally even till the beginning of convalescence. (3) Reactions that increase greatly in strength from the early stage of the fever and diminish after convalescence has become established are highly significant ; those remaining at the same strength throughout the illness can be ignored. The former are called rising-titre reactions ; the latter are constant-titre reactions which occasionally occur in other diseases. Low-titre reactions may occur in healthy pregnant women. (4) The reaction should be tested repeatedly : the rise in the titre from negative or 1–25 near the onset to 1–100 within a few days rarely occurs in any disease except one of the fevers of the typhus group. (5) The reaction must be interpreted in the light of the clinical features, and not as the sole diagnostic criterion. (6) The strength of the reaction has no constant relationship to the severity of the disease ; it may be weak or negative in very mild or very severe attacks. (7) A bacillary suspension of proved reliability must be used. (8) The reaction is positive in flea typhus and in many cases of tick typhus. Complement-fixation or rickettsia-agglutination tests are sometimes needed to differentiate these diseases from louse typhus, but facilities for carrying out these tests are not generally available.

German physicians, who have had great recent experience of the disease, make extensive use of several simple modifications of the Weil-Felix test for bedside diagnosis. A droplet of serum mixed with a drop of *Proteus OX*19 suspension on a glass slide will give the reaction within a few minutes ; the slide is gently tilted at intervals, and in positive cases clumping can be seen with the naked eye or a hand lens. A droplet of fresh blood from the finger can be used in the same way, and the reading can easily be made if the bacillary suspension has been lightly stained by adding a little methylene blue solution.

Droplets of blood can also be made into thick films on a slide and dried in the air. To each of these a different quantity of bacillary suspension is added and the slide is tilted to and fro. In positive cases clumping occurs within ten minutes. This method is specially suitable when surveys of suspected communities are being made, the labelled films can be examined at any time up to a week or so.

These rapid tests seldom disclose reactions weaker than 1–100, and they should be checked in all doubtful cases by standard tests.

In spite of their limitations they have been very favourably reported

on by many physicians ; they often give the diagnosis at once, and daily tests can easily be carried out.

For the differential diagnosis of louse typhus and the other fevers of the typhus group (*see* p. 185).

Prevention

Thorough louse control is the basis of success in the prevention of typhus fever, just as it is in relapsing fever (*see* p. 103).

The first step should be the disinfestation of the patient and his clothing by dusting with a 5 or 10 per cent. D.D.T. powder. He should then be taken to an isolation hospital where, before admission to the ward he is bathed, shaved, and washed with a disinfecting solution to kill rickettsiæ deposited on the surface of the body in the form of louse fæces. The clothing is also disinfected and clean clothing impregnated with D.D.T. is provided. Those who have come into contact with the patient should be well dusted with the D.D.T. powder and so should their bedding and clothing.

Persons engaging in preventive work should be given protective inoculation beforehand ; they must wear protective clothing impregnated with D.D.T. and keep themselves constantly dusted with the powder. Persons under thirty years old should be employed ; the risk to older persons is much greater unless they have had recent attacks.

Diagnosis plays an important part in prevention ; if the initial cases are missed much precious time is wasted. An attitude of watchful suspicion on the part of the doctor is therefore essential.

Protective Vaccines. These are of two main types : (1) Live vaccines, consisting of the living rickettsiæ of flea-borne typhus obtained from the tissues of infected animals or from the fæces of infected fleas, and attenuated in various ways. Enormous numbers of persons have been vaccinated in French North Africa, and excellent results have been claimed ; but other workers have reported alarming reactions, some of them fatal. The vaccines are not strictly specific, being made from *Rickettsia mooseri*, and they are not generally regarded as being reliable or safe.

(2) Killed vaccines were used on a large scale in the second world war. There are three main types, all of which consist of killed suspensions of *Rickettsia prowazeki*. The earliest was Weigl's vaccine, made from the guts of artificially-infected lice, but its preparation is so complicated and expensive that it has been largely superseded by two other types. Durand and Giroud's vaccine is made from the lungs of mice or rabbits which have been inoculated intranasally with highly virulent cultures of the rickettsia. The Cox and Cox-Craigie vaccines, used by the Allied armies, are made of yolk-sac cultures obtained by inoculating embryo chicks during the process of incubation. A few days after inoculation the yolk sacs contain enormous numbers of

rickettsiæ ; these vaccines give a high degree of protection by greatly reducing the severity of any attacks that occur in vaccinated persons.

E. Ding (1943), a German military doctor who was also a storm-troop leader, reported that large groups of human beings were vaccinated *with six different types of killed vaccines and that six to eight weeks* later all of them had attacks of typhus which could only have resulted from experimental inoculation. Each group appears to have consisted of at least 200 persons because the percentage of complications in one group is stated to have been 0·5. Among the persons who had been vaccinated with the killed vaccines there were no deaths, the average duration of the fever was ten to twelve days, and the average incubation period was six to seven days. In two control groups, consisting of about the same numbers of unvaccinated persons, the fatality rates were 33·3 per cent. and 20 per cent. respectively, the average duration of the fever was seventeen to eighteen days, and the average incubation period was two to three days. No mention is made of the source from which this extensive human material was obtained for the experiments which have rightly been described as " crucial." The vaccines obviously did not protect against virulent infection, but gave complete protection against fatal results.

The vaccines are given in three doses at weekly intervals, the reactions are not severe; single doses are given every six months to persons exposed to continued risk of infection after the primary vaccination.

Treatment

The new antibiotic drugs, chloramphenicol (chloromycetin) and aureomycin are effective in the treatment of louse typhus and of the other typhus-group fevers ; unfortunately they are very costly. Differences of opinion exist with regard to the doses needed ; the drugs are given by the mouth in initial doses of 1·0–3·0 gm., followed by 0·25–0·5 gm. every four to six hours till the temperature has remained normal for twenty-four hours. If the temperature should rise again a further course is given. In cases treated within the first four or five days of the illness initial doses of 1·0–1·5 gm. followed by 0·25 gm. every six hours can be given, but the dosage should be increased if the response is not satisfactory, and in any case the treatment should be continued for two to three days after the temperature has fallen because recrudescence is more likely to occur after early than after later treatment.

Nausea and vomiting occur in some cases but are seldom so troublesome as to necessitate omission of the drug ; milk given with each dose is said to be useful in preventing these troubles.

Even if only small quantities of the drugs are available, such as 4·0 gm., these should be given in divided doses for one day and good results will often follow.

Para-aminobenzoic acid is less effective than the above drugs but is of distinct value if given early in the illness; 2·0–4·0 gm. are given by the mouth every four hours, and enough bicarbonate of soda is given to keep the urine alkaline.

German physicians advocate the use of cardiovascular tonics such as camphor, strophanthin and digitalis.

For severe headache, pains or insomnia, chloral hydrate is still favoured, in doses of 15–40 grains.

Pneumococcus pneumonia and septic complications are not likely to occur in patients treated with the new antibiotics. Penicillin, when suitable, is preferable to the sulphonamides for secondary infections.

Convalescent serum, convalescent blood, and the sera of immunized animals have been favourably reported on, but they are not likely to be available except in special conditions and there are obvious risks connected with their use.

Skilled nursing, plenty of liquids, and a light nutritious diet, rich in all the vitamins, are essential. Subcutaneous salines are strongly recommended by some observers in cases of pronounced dehydration.

Frequent changes of position are needed for unconscious patients. Drinks and liquid diet should be given through nasal tubes to patients who cannot swallow, but conscious patients should be encouraged to take their nourishment while propped up by a bed-rest or even sitting up. Regular meals and thorough mastication of simple forms of solid diet can be encouraged among fully conscious patients.

The general management of the cases is on much the same lines as in typhoid fever.

After severe attacks the patients must be kept under skilled medical supervision for a month or more, and it must be remembered that prolonged rest is needed because of the damage that is caused to the myocardium and blood vessels.

BRILL'S DISEASE

Hundreds of sporadic cases of relatively mild louse typhus have been reported from New York since 1898 when Brill first described this disease whose ætiology was much disputed till Zinsser showed that the cause was *Rickettsia prowazeki* and that 95 per cent. of the patients came from European countries in which louse typhus was endemic. The disease is regarded as a very late-relapsing form of louse typhus occurring among persons in whom the rickettsiæ have persisted indefinitely after the original attacks. Isolated cases have recently been reported from European countries among persons known to have suffered several years previously from attacks of louse typhus.

Although rickettsiæ have often been isolated from patients, spread of infection to " contacts " has not been known to occur.

FLEA TYPHUS

(Synonyms: Flea-borne typhus, endemic typhus, murine typhus, ship typhus, urban tropical typhus.)

Definition. A zootic typhus fever caused by *Rickettsia mooseri* which is transmitted to man from infected domestic rats by rat fleas, especially by *Xenopsylla cheopis*.

History. In 1926 Maxcy suggested that a sporadic typhus-like fever occurring in North America might be transmitted from infected rats to man by fleas.

In 1931 Dyer and others transmitted infection to guineapigs by the bites of fleas found on rats trapped in infected localities.

In 1932 Nicolle described " murine typhus," a fever occurring in French war vessels in Toulon Harbour ; he held that the infection was conveyed by rat fleas from infected rats.

Although the disease has not long been recognised, it has already been found to be endemic in many parts of the world, and several forms of fever which had previously been regarded as of unknown ætiology are now known to be flea-borne typhus.

The fever is generally regarded as being a zootic disease of rats, and as not being transmitted from man to man. Moöser and some other workers hold that when a person has been infected with *R. mooseri* by rat fleas the rickettsiæ can then be transmitted from the patient to other persons by human lice and so give rise to louse-borne typhus. If this transmutation of the disease ever does occur it must be quite exceptional because in the thousands of cases of flea-borne typhus which occur yearly in the U.S.A. there has been no recorded example of transmission of infection from a patient to other persons. The same is true of many other places in which flea typhus is prevalent in the complete absence of louse-borne typhus ; it is only in Mexico and one or two other countries that flea-borne typhus has been suspected of having given rise to the louse-borne disease, and it seems possible that in these places the two diseases may have occurred simultaneously.

Although recent investigations support the view that flea typhus and louse typhus are different diseases, it is safer to assume that the rickettsia of flea typhus may in certain conditions be transmitted by human lice so that it is a wise precaution to disinfest every patient who harbours lice even when he is known to be suffering from flea-borne typhus.

Transmission from rat to rat and from rat to man is believed to occur occasionally by swallowing food contaminated with infected excreta of rats or mice.

Geographical Distribution. This corresponds closely with the distribution of the rat-flea, *X. cheopis*, and so is almost universal in tropical and sub-tropical climates in which hot and moist weather

persists for a considerable part of each year. The best known foci are in tropical and sub-tropical America,. Asia and Australia; in South Europe and the whole of Africa.

TYPHUS LIKE FEVERS

(Conveyed by ticks or other arthropods).

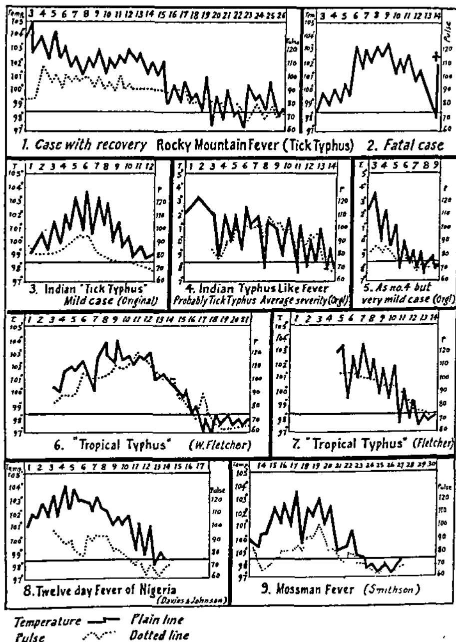


FIG. 34. Temperature charts of typhus-like fevers.

In many places the existence of the disease has not been detected till recently.

Ætiology. The rickettsia, *R. mooseri*, is closely related to *R. prowazeki* but is less virulent to man and more virulent to rats and

guineapigs, and transmission is almost entirely by *X. cheopis* whose presence is essential for the maintenance of infection among rats which form the reservoir of the disease in the infected foci.

Pathology. Little is known of the morbid changes in the human tissues as the disease is rarely fatal, but the lesions in infected animals are very similar to those caused by *R. prowazeki*.

Symptoms. These are the same as in mild louse typhus, the only reliable means of clinical differentiation is by agglutination and complement-fixation tests in which the rickettsiæ of the two diseases are used as antigens. In most cases the onset is more gradual and the rash less pronounced than in louse typhus. The temperature tends to be more remittent in type. Death seldom occurs except in elderly and debilitated persons.

In Mexico a fatal form of the disease is said to exist, with a mortality rate of 40 per cent., but this is so unusual that some observers suspect that the virulent outbreaks in that country are louse-borne typhus.

Diagnosis. Cases of flea typhus are not likely to be diagnosed unless the disease is known to be endemic in the locality and routine Weil-Felix tests are carried out in all attacks of continued fever lasting more than a week. A rising-titre *Proteus OX*19 reaction is very suggestive of flea typhus when the clinical features are consistent with the diagnosis and there are good reasons for excluding louse-borne and tick-borne typhus fevers in both of which the Weil-Felix reaction may be of the *OX*19 type. An enquiry into the epidemiological conditions in which infection has occurred will usually help to exclude these two diseases but in some cases a definite diagnosis is impossible without the aid of the complement-fixation or rickettsia-agglutination tests which, unfortunately, are not generally available. For the differentiation of flea typhus from the other fevers of the typhus group the note on p. 185 should be consulted.

Prognosis. Apart from the doubtful Mexican type the fatality rate is seldom more than 5 per cent. Deaths are rare except in old and debilitated persons.

Prevention. This is on the same lines as for bubonic plague. In heavily-infected localities the use of a vaccine might be considered, but thorough dusting of the haunts of the rats with D.D.T. followed by trapping or poisoning the rats and rat-proofing the premises are effective measures.

TICK TYPHUS

Definition. Tick typhus is the zootic fever of the typhus group which is transmitted by ticks. It is caused by *Rickettsia rickettsi.*

About thirty different synonyms have been employed as designations for varieties of the disease so that the literature of the subject is very confusing to the uninitiated reader.

The classical form of the disease, Rocky Mountain spotted fever, which was well known long before the existence of the fever in other parts of the world was suspected, is unhappily named because the words "Rocky Mountain" suggest that the disease occurs only in one locality. Observers in other places have naturally been deterred from classifying their cases under a heading which was so obviously unsuitable.

Another cause of confusion is that the disease shows a great degree of variability. Although some of these variations are striking, they are more apparent than real; most of them occur in the classical form of the disease, Rocky Mountain spotted fever, and they can be explained as being due to differences in the virulence of strains of the rickettsiæ, differences in the mechanism of transmission by various kinds of ticks, and other variations such as commonly exist in connection with diseases transmitted by arthropods. All the evidence tends to show that one species of rickettsia is concerned in the causation of tick typhus, and that the disease itself is essentially the same in whatever part of the world it occurs.

The variations that occur do not justify the use of different names, but there is no objection to the use of an additional name to indicate the existence of some special feature that is of diagnostic significance; for example, it may be helpful to describe a variety of the fever as "the boutonneuse type of tick typhus."

It may be mentioned that some American workers do not classify tick typhus as a fever of the typhus group; they regard its organism as belonging to a different genus from the "true" rickettsiæ and call it *Dermacentroxenus rickettsi*. The reason for this distinction is that the organism is often found inside the nucleus of the invaded cell. In other parts of the world the disease is generally regarded as a member of the typhus group and the organism is called *R. rickettsi*. Recent observations by Parker and Castañeda, both of whom are American workers, have shown that there is a pronounced degree of immunological relationship between the rickettsiæ of louse-borne and tick-borne typhus; these findings as well as the similarity of the two organisms in other respects, and the general resemblance of the diseases caused by them, seem to be a complete justification for placing tick typhus in the typhus group. From the clinical point of view the classification of the fevers in the same group greatly helps the student to obtain a clear mental picture of the two diseases.

Rocky Mountain spotted fever was the first of these fevers to be discovered, it has also been much more closely studied than the others, and therefore can be regarded as the standard type. The other forms can best be described by mentioning the points in which they differ from the Rocky Mountain fever.

ROCKY MOUNTAIN SPOTTED FEVER OR ROCKY MOUNTAIN TICK TYPHUS

Definition. This is primarily a disease of rodents or other animals of the wilds, it is caused by *Rickettsia rickettsi*, which is conveyed from infected animals to man by certain ticks, especially *Dermacentor andersoni*. The disease in its clinical and pathological aspects has a general close resemblance to louse-borne typhus fever.

History. The disease has been known for a long time in certain regions of the Rocky Mountains.

In 1904 Wilson and Chowning found that the infection was conveyed to man from rodents of the wilds by the bite of ticks.

In 1909 Ricketts described the bodies which are called by his name; he found them in infected ticks.

The pathology of the disease was described by Wilson and Chowning in 1902, and more completely by Wolbach from 1918 to 1922.

R. R. Parker, R. R. Spencer, W. W. King and others have made important recent contributions to the knowledge of the disease. The following account is largely based on the writings of R. R. Parker.

Geographical Distribution. Till 1931 the disease was regarded as being confined to the Rocky Mountain and Pacific Coast States of the U.S.A.; since that year it has been reported from nearly all the States of the U.S.A. The disease tends to persist in certain localities, but is liable to die down in some of these or to spread to other areas. Outdoor workers are chiefly affected, but a few cases have been reported in town dwellers; probably in the latter cases the infection has been imported by dogs which have become infested by ticks in the endemic areas.

The disease usually occurs in sporadic form, but a few small local outbreaks have been reported.

Seasonal Distribution. Most of the cases in the Rocky Mountains occur in April and May when the ticks are most active; at higher altitudes and in the Eastern States the disease is most prevalent in the autumn.

Ætiology. *R. rickettsi*, the cause of the disease, is closely related to *R. prowazeki* in its morphology, staining reactions and cultural properties. It differs in the following respects: (1) it is transmitted by ticks from lower animals so that it causes a zootic disease; (2) it is often found inside the nuclei of the cells in which it lives; (3) the disease caused by it in inoculated guineapigs does not completely immunize the animals against inoculation with *R. prowazeki*; (4) it usually causes a severe and often fatal disease in experimental guinea-pigs; and (5) the disease caused in human beings is different in some respects from louse-borne typhus.

Various animals, chiefly small rodents, are susceptible; and these have been regarded as the reservoirs of infection, which is maintained in them chiefly by the bites of infected larval and nymphal ticks.

Infected female ticks can transmit the rickettsiæ through the egg to their progeny for several generations, and perhaps indefinitely, so

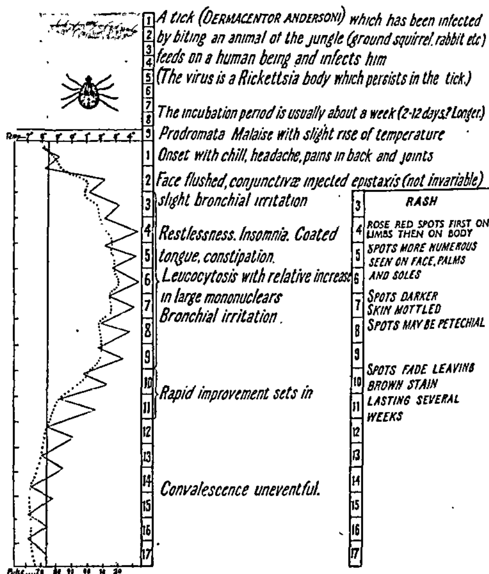


FIG. 35. The story of Rocky Mountain fever (tick typhus).

that the most important natural reservoir of infection must be the ticks themselves.

Even in places where the disease is prevalent only a small proportion of ticks of the vector species are found to be naturally infected, usually 1 or 2 per cent., and rarely as many as 5 per cent. Unless the ticks are examined in the immediate neighbourhood in which the disease

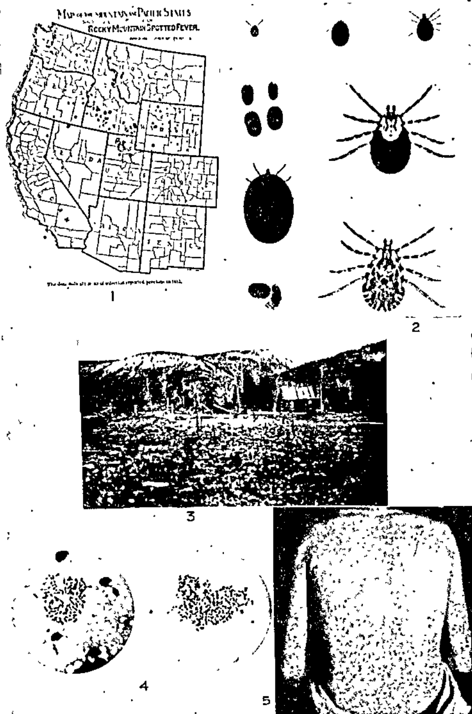


FIG. 36. Illustrations of Rocky Mountain fever.

1. Map of case distribution in United States (U.S. Public Health Reports, 1915). 2. *Dermacentor andersoni*. 3. Typical infected farm. 4. Smears of intestinal contents of infected ticks, showing Rickettsiae. 5. Rash on body.

is actually prevalent at the time, it is quite exceptional to find evidence of infection among the ticks.

Infection is usually transmitted to man by infected adult ticks, and it is believed that the tick must remain fastened for several hours before the rickettsiæ can find an entrance into the body.

There are wide variations in the virulence of different strains of the rickettsiæ ; in some localities the fatality rate may be 60 per cent. whereas in others not far away it may be as low as 10 per cent. Even in the same locality the rate may fluctuate from year to year, being 10 per cent. in one year and 30 per cent. in another.

The virulence of infection in different attacks in the same place also varies greatly, this is probably due to variations in the conditions in which transmission occurs ; starved ticks are known to be much less infective than ticks that have recently had a blood meal.

Infection usually enters through the puncture made by the tick in the act of biting, but it can also enter through the conjunctiva when the eyes are rubbed by a finger which has become infected through handling ticks from dogs. It can also enter through abrasions or even through the unbroken skin.

Pathology. The lesions found in the body differ in no important respect from those of louse typhus.

Symptoms. These also correspond closely to those of louse typhus so that in many cases it is impossible to differentiate the two diseases on clinical grounds. In most cases of tick typhus the fever curve shows deeper remissions and a more gradual decline in the temperature ; the rash is more conspicuous ; the spots tend to appear first on the extremities ; they usually spread to the palms, soles and face ; and they are often elevated. Apart from these points the description of the symptoms of louse typhus holds true for tick typhus.

The incubation period is two to fourteen days, sometimes longer ; the shorter it is the more severe the attack is likely to be.

There may be no positive evidence of a bite by a tick, but occasionally there is a spot of induration at the site of the bite, and also some local lymphangitis.

The onset is like that of louse typhus and so are the early symptoms ; the temperature usually rises rather more slowly and the daily remissions are greater.

The rash can sometimes be detected on the wrists and ankles as early as the second day ; it is usually pronounced on the extremities by the third to the fifth day, but it may be delayed till the sixth or seventh day ; it soon spreads all over the body, including the palms, soles, and face. The spots are discrete, they tend to be larger and more raised than in louse typhus ; at first they are bright red and fade on pressure, soon they become dark-red and cease to fade on pressure. They are often petechial. In mild cases there may be only a few spots or none at all. Brown staining at the sites of the spots often persists

for several weeks and may simulate a syphilitic rash. In the most severe cases the rash is often profuse and hæmorrhagic.

The continued-fever stage and the march of the symptoms are like those of louse typhus, but *the daily remissions tend to be more pronounced* and towards the end of the attack the fever may be intermittent.

The nerve-system symptoms, blood changes and complications are as already described in the section on louse typhus.

The types described by Parker are : (1) Ambulatory attacks with little or no rash and with low remittent or intermittent fever lasting one or two weeks ; (2) abortive attacks with sudden onset, a rapid rise of temperature to 103° or 104° F., a fleeting rash, and a total duration of a week or less ; (3) typical attacks lasting two to three weeks ; and (4) fulminating attacks with death within three or four days.

Diagnosis. This is easy in typical cases occurring in places where the disease is known to exist. When suspicion of the existence of the disease in the locality is not aroused a wrong diagnosis is usually made. The character of the rash, especially its distribution, is often highly significant. The sporadic occurrence of a fever with rapid onset and pronounced nervous symptoms, in a place where a tick is likely to have bitten the patient, should suggest tick typhus as a possible diagnosis.

The Weil-Felix reaction is sometimes the same as in louse typhus, but it is sometimes negative, or the reaction to *Proteus OX*2 may be stronger than that to *Pr. OX*19 ; in fact, any type of reaction to the *proteus organisms may occur except one of the Pr. OXK type.*

If the rickettsia-agglutination test or the complement-fixation test can be carried out a confident diagnosis will usually be possible.

A positive Widal reaction does not exclude tick typhus, especially in patients who have been inoculated against typhoid fever.

The history of a bite by a tick within the incubation period or the presence of a tick still attached at the onset is highly significant.

A history of exposure to the risk of tick bite or of the handling of ticks from dogs or other animals may be a clue to the diagnosis.

Prognosis. The case-fatality rate varies so greatly in different places, and in the same place at different times, that no general statement can be made about the severity of the disease. Each case must be judged on its own merits, and the rules laid down for louse typhus can be taken as a guide.

Treatment. This is the same as for louse typhus, but no special precautions are needed to prevent the spread of infection from the patient. Chloromycetin (chloramphenicol) and aureomycin are equally effective in both diseases.

Prevention. If infected areas cannot be avoided, tick-proof clothing impregnated with dimethyl phthalate should be worn. Sitting or lying down on the ground is risky.

The body should be carefully examined at frequent intervals and

any attached ticks should be removed after applying a drop of tincture of iodine to the site of the bite. If a tick is firmly attached a small portion of the skin, including the biting apparatus of the tick should be snipped off with scissors. Early removal of ticks greatly reduces the risk of infection.

Yolk-sac vaccines are now available; they greatly reduce the severity of attacks of the disease though they do not give complete protection against the risk of infection.

OTHER VARIETIES OF TICK TYPHUS

Tick-borne fevers of the typhus group are now known to occur in many parts of the old and new world. Many special names have been given to them because they were thought to be new diseases.

The more closely these fevers are studied the more likely it seems that they are merely different varieties of tick typhus.

BOUTONNEUSE FEVER

This variety of tick typhus was described by Conor and Brugh in 1910 as an " eruptive fever " of unkown ætiology occurring in Tunisia. It was later found to be caused by a rickettsia which was transmitted from lower animals to man by a tick, *Rhipicephalus sanguineus*, the common dog tick. The disease is much milder on the average than Rocky Mountain spotted fever, and in most cases there is a local sore at the site of the tick bite and an associated lymphangitis. Inoculated guineapigs get very mild, or even "inapparent", attacks which do not confer complete immunity against inoculation with the rickettsia of Rocky Mountain spotted fever. Because of these differences the rickettsia has been regarded as belonging to a different species and has been called *R. conori*. But Parker (1943) has recently found a strain of the Rocky Mountain rickettsia against which the organisms of boutonneuse fever and of African tick-bite fever give complete immunity, so it is safe to assume that all three rickettsiæ are merely different strains of *R. rickettsi*.

The local sore, called the *tache noire*, does not always occur; it corresponds to the eschar of mite typhus and just as happens in that disease it may be present or absent in varieties of infection which have been proved to be caused by the same species of rickettsia.

Boutonneuse fever can therefore be regarded as a mild variety of the same disease as Rocky Mountain spotted fever.

It occurs in most of the countries round the Mediterranean Sea as a mild sporadic disease. Cases have been reported from various places in tropical Africa.

The **Tick-Bite Fever** of South Africa and the **Tick Typhus** of Kenya are also local varieties of tick typhus which differ in no essential respects from mild varieties of Rocky Mountain spotted fever. Gear's

studies of tick-bite fever have done much to throw light on this much debated problem.

TICK TYPHUS IN INDIA

Tick typhus in India is not different in any essential respect from the disease in other parts of the world. The first case to be recognised as being probably a mild form of Rocky Mountain spotted fever occurred in 1916 and was described by the present writer, who was also the patient, in 1917. The attack occurred after a bite by a tick in the Kumaon foot-hills of the Himalayas. The tick had been attached for more than fourteen hours without being observed, and was not identified because it was then believed that no human disease in India was transmitted by ticks, but the clinical and epidemiological features of the attack pointed strongly to a disease related to, if not the same as, Rocky Mountain spotted fever, and in a further paper in 1921 the suggestion was made that these and other typhus-like fevers transmitted by ticks should provisionally be classified as tick typhus.

During the next few years similar cases were reported from different parts of India ; in some of these the association with tick bite was definite, in others there was no evidence of a bite but only a history of exposure to risk of such a bite ; and doubtless some of these were cases of mite typhus, a disease which was not recognised in India because Japanese writers described a primary local lesion and lymphocytosis as essential features of tsutsugamushi fever.

In 1935 Boyd described the results of a systematic study of the typhus-like fevers in India ; he carried out Weil-Felix tests of the sera of all such cases admitted to the military hospitals of India and classified them according to the type of reaction with *Proteus XK*, *P. X2* and *P. X19*. Among ninety-two cases he found that thirty-five reacted only with *XK* ; fourteen reacted strongly with *X2* and weakly with *X19* ; the remaining forty-eight reacted with *X19*, but these cases fell into two groups in one of which (sixteen cases) the reaction was + or ++ and the clinical features as well as the climatic and geographical distribution corresponded closely to those of the cases of the *X2* group, whereas in the other group (twenty-seven cases) the reaction was *X19* +++ and the features of the disease were different from those of the other three groups. The findings are of such interest that they are shown in a table from which the only relevant item excluded is the one showing the geographical distribution of the four types, but this shows a close agreement between Groups II and III and a significant difference between them and Groups I and IV.

There was no clear evidence of the types of vectors concerned in the transmission of any of the cases so that the classification is purely serological, but viewed retrospectively it is safe to assume that the *XK* group consisted of cases of mite typhus, and that Group IV (*X19* +++) corresponded to flea typhus, because louse typhus

could be excluded. Groups II and III are of special interest, they obviously form a homogeneous group and the data referring to their clinical features, seasonal and geographical distribution suggest that they were cases of tick typhus, and if so there were thirty cases of this disease.

Group	I (*XK*)	II (*X*2).	III (*X*19).	IV (*X*19).
Types	*XK* +++. *X*2 and *X*19 −	*X*2 +++. *X*19 +. *XK*±.	*X*19 + to ++. *X*2 and *XK* ±	*X*19 +++.
Seasonal incidence (maximum).	August and September.	December.	December.	Throughout year except in February, March and April.
Rash : in British	15/21.	8/8.	10/10.	5/6.
in Indians	1/14.	5/6.	6/6.	1/21.
Day on which rash first seen.	5th to 7th.	3rd or 4th.	3rd.	4th to 10th.
Type of rash	Flush ; macules.	Macules ; papules ; petechial.	Macules ; papules ; petechial.	Maculo-papular.
Distribution of rash	Trunk only.	Generalised.	Generalised.	Trunk and limbs.
Duration of rash in days.	7.	14·4 to 18·4.	10·5 to 25,	3 to 4.
Staining after fading of rash.	*None.*	*In some cases.*	*In some cases.*	*Not mentioned.*

This view is strongly supported by a study of Seaton and Stoker who, in 1946, carried out complement-fixation tests of forty consecutive sera from military hospitals in India in which the Weil-Felix reactions were of the *OX*19 or *OX*2 types ; they found that eighteen of the sera were positive with murine (flea) typhus antigen and sixteen were positive with Rocky Mountain spotted fever antigen obtained from Cox.

Strains of *R. rickettsi* have been isolated by Kalra in the Kumaon Hills and by Seaton in the Bombay Presidency, so that the occurrence of tick typhus in India is no longer doubtful.

The reason for entering into a detailed discussion of the disease is that it serves as a good example of the general problem of the recognition of tick typhus.

TICK TYPHUS IN SOUTH AMERICA

A highly virulent form of tick typhus has been discovered to exist in Brazil and Colombia. The fatality rate is usually 90 per cent., but milder cases may occur without being detected. About twelve different names have been given to this variety of the disease, such as "exanthematic typhus of Brazil," "spotted fever of São Paulo" and "South-American rickettsiasis." The cause of the disease has been proved to be *R. rickettsi*, identical in all respects with virulent strains of the organism of Rocky Mountain spotted fever. A similar disease is now known to occur in Mexico.

Differential Diagnosis of Tick Typhus

Sporadic cases of typhus-like fever occurring in any part of the world, in conditions in which a bite by a tick is likely to occur, should always arouse suspicion of tick typhus ; but the differentiation of the disease from the other fevers of the typhus group often gives rise to great difficulty even when there are *facilities for investigation* by animal experiments. If the rickettsia-agglutination and complement-fixation tests are available they will solve the problem of diagnosis. In the meantime the type of the rash is often helpful ; the spots are usually conspicuous, they appear first on the extremities and are often pronounced on the palms, soles, and face. An enquiry into the *epidemiological conditions of occurrence should always be carried out ;* this will often point to the likelihood of transmission by ticks rather than by fleas or mites, and in many parts of the world mite transmission can be ruled out with reasonable certainty.

In places in which mite typhus is a possibility a strongly positive reaction to *Pr. OXK* with a negative to *OX*19 and *OX*2 is in favour of that disease. So also a strongly positive reaction to *OX*19 with a negative to *OX*2 and *OXK* suggests flea typhus, but the reactions are often ambiguous.

See p. 185, where the differential diagnosis of the typhus group fevers is discussed.

MITE TYPHUS

Synonyms. Tsutsugamushi disease, Japanese river fever, scrub typhus, tropical typhus of the rural type.

Definition. A zootic fever of the typhus group caused by *Rickettsia tsutsugamushi* (*R. orientalis*) which is transmitted to man from lower vertebrates, chiefly rats and voles, by larval mites.

History. The disease was described in the third century A.D. by a Chinese writer, who stated that it was caused by " a small red insect," presumably a mite.

The classical form of the disease has long been known in Japan under the name tsutsugamushi (dangerous insect) disease. The Japanese writers described an initial local sore, with associated lymphadenitis, and with lymphocytosis, as essential features of the disease so that observers in other countries in which these features rarely occurred in outbreaks or cases believed that they were dealing with a new disease to which such names as " pseudo-typhoid of Deli " (in Sumatra), " coastal fever of Queensland," " Sumatra mite fever " and " rural tropical typhus " were given.

The identity of the last-named disease with tsutsugamushi disease was finally established by Lewthwaite and Savoor about 1940.

In 1918 Kitashima and Hiyajima showed that the " red mite " was a vector. In 1922 Hayashi described the rickettsia and called it *R. tsutsugamushi.*

Distribution. The disease has a widespread distribution in Oriental countries ; it has not been clearly proved to occur anywhere west of India and Kashmir, though its occurrence in Ethiopia and Central Africa has been suspected.

The chief foci of infection are in India, Ceylon, Burma, Malaya, Indo-China, the Dutch East-Indies, New Guinea, Eastern China, Japan, the Philippines and North Queensland. (See fig. 37).

Until the outbreak of the war with Japan the disease was regarded as being of importance only among outdoor workers in certain areas

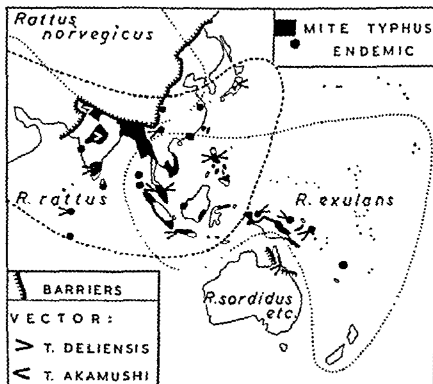


FIG. 37. The recorded distribution of mite typhus, the vector *Trombicula akamushi* sensu lato in two forms, and native races of rats. (Audy and Harrison, Trans. Roy. Soc. Trop. Med. & Hyg. 44. 4. 1951.)

in Japan, Malaya, the Dutch East Indies, North Australia, etc., where sporadic cases and small outbreaks were known to occur. When bodies of troops began to operate in the open, often uninhabited, localities in which infected mites were present outbreaks of the disease were frequent and mite typhus soon became one of the most important and most dreaded diseases of the war against Japan.

After a military exercise lasting five days in scrub and forest country in Ceylon in December, 1943, about 750 cases occurred among the troops engaged, although the existence of the disease in Ceylon had hardly been suspected. The fatality rate was less than 2·0 per cent., but in other outbreaks in places in the South Pacific and South-East Asian areas the rate was often as high as 10–20 per cent.

Ætiology. The causative rickettsia, *R. tsutsugamushi*, primarily infects rats or voles among which it is transmitted by larval mites of two related species, *Trombicula akamushi* and *Trombicula deliensis*; the larvæ are very small, about one-hundredth of an inch in length; they feed only once on their vertebrate host; in the later stages of their life they do not bite again but live on organic matter in the soil. The same mite, therefore, cannot both acquire and convey infection; what happens is that when a female mite becomes infected it transmits the rickettsiæ through its eggs to the offspring, which in the larval stage infect the animals on which they feed. Human beings become infected by the bites of infected larvæ but patients can very rarely, if ever, play any part in maintaining the infection because they are not at all likely to be bitten by mites during their illness, and even if this should happen the offspring of the infected larvæ would seldom have an opportunity of feeding on a susceptible person.

Knowledge of the mode of transmission among lower animals is of practical importance; these animals and the mites which are attached to them are not sources of immediate risk to persons who enter their haunts; the risk is from larvæ which are seeking a host for their one and only meal so that rat destruction may even increase the danger of infection by depriving the free-living infected larvæ of their normal source of nourishment and compel them to attack human beings. When larval mites feed on man they remain attached for two or three days, causing little or no irritation so that their presence is seldom suspected and often there is no history of bite by mites in cases of the disease.

Epidemiology. The conditions favouring the presence of infection are moist grass and other vegetation infested by rats or voles and the vector mites. The grassy banks of streams, the fringes of forests and abandoned plantations or cultivated grounds are favourite sites for the rodent reservoirs of infection and the vector mites.

The seasonal incidence varies; in some places conditions favourable for transmission exist throughout the year, but usually the larval mites are most abundant and active during and after wet weather.

Pathology. Apart from the frequent presence of the local primary lesion, called the eschar, with the associated lymphadenitis and lymphangitis, the pathology of the disease is essentially the same as in louse typhus; the resemblance to tick typhus is even more pronounced because in some forms of that disease there is a similar primary local lesion.

Symptomatology. The local lesion, when it occurs, begins as a papule or macule which appears two or three days after the bite by the infecting mite, and at the place at which the mite attached itself; the papule enlarges and its centre becomes necrosed; then a slough is formed; this falls off leaving a small punched-out ulcer surrounded by a narrow zone of inflammation; the ulcer heals about two or three

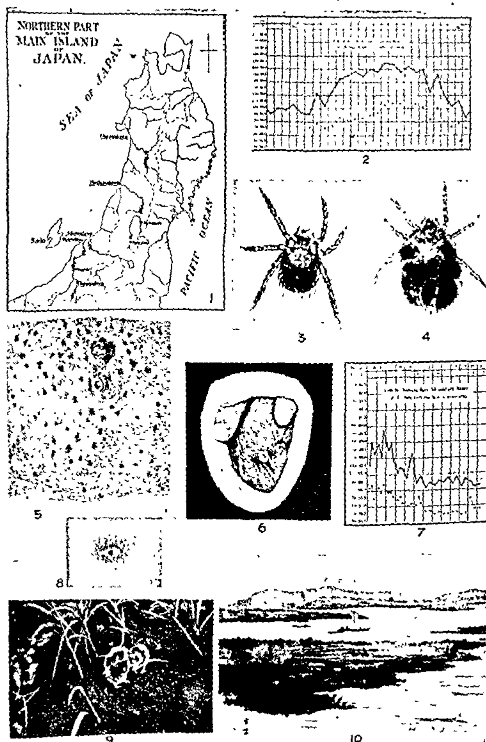


FIG. 38. Illustrations of Japanese river fever or mite typhus.

1. Map showing riverine sites (dotted) of the disease in Japan. 2. Temperature chart. 3 and 4. *Larval mites (greatly magnified).* 5. *Ulcer and roseola* over breast on seventh day. 6 and 8. Local lesions. 7. Temperature chart. 9. Field mice, reservoirs of infection. 10. Infected locality.

weeks after the bite, and a small depressed scar is left. There is little or no pain, and often the lesion does not progress beyond the initial papular stage which is often overlooked unless a careful search is made. A clue to its presence is the occurrence of an associated local lymphadenitis which is seldom absent when the eschar is fully developed and is often present even when there is only a small papule.

The eschar is usually single, but there may be two or more ; as many as six have been found. The site of the eschar varies with the kind of clothing worn at the time of the bite and according to whether the person has been sitting, standing, or lying down when attacked.

The incubation period of the fever ranges from five to twenty days. The general course of the illness is so like that of other fevers of the typhus group of corresponding severity that a differential diagnosis is often impossible on purely clinical grounds unless there is an eschar and even this does not help to differentiate the disease from the variety of tick typhus in which there is a similar local lesion.

The description of the signs and symptoms of louse typhus should be consulted ; it applies equally to mite typhus except in the following respects : in mite typhus there may be a local lesion ; generalised lymphadenitis is more pronounced ; the average severity is less ; the onset is often less rapid ; the rash is seldom petechial ; the fever is often remittent in type ; leucopenia occurs more frequently and the termination is often by more gradual lysis.

The complications and pathology of the two diseases are very similar so that no separate description is needed.

Although the above clinical differences are seldom enough by themselves to justify a differential diagnosis, difficulties seldom arise.

Serology. In the great majority of cases mite typhus is easily diagnosed by the type of the Weil-Felix reaction. With a reliable suspension of *Proteus OXK* a rising-titre reaction occurring in a typhus-like fever is very strong evidence of mite typhus. The titre may begin to rise before the end of the first week but often the reaction does not occur at a significant titre, till the end of the second week, or even till convalescence has set in, so that the test is not very helpful for the early diagnosis of doubtful cases.

Complement-fixation tests suffer from the same drawback, and on the whole are less satisfactory than in other rickettsial fevers owing to the differences that occur in the antigens of different strains of *R. tsutsugamushi*, even in cases occurring in the same area. On the whole the *Proteus OXK* reaction is the most useful test, especially as it is rarely positive in any other rickettsial fever.

Diagnosis. Unless the disease is known to occur in the locality and the patient is known to have been exposed to risk of infection suspicion is not likely to be aroused till the rash appears, except in cases in which the eschar is detected, and the rash can easily be overlooked or it may not be visible. Even to-day it can safely be

asserted that the great majority of the cases occurring in peace-time conditions are not recognised. When suspicion is aroused the discovery of the eschar will usually justify an immediate diagnosis at the onset of the fever in the Oriental countries in which the disease occurs. With the appearance of the rash a diagnosis of a typhus-group fever becomes possible, but differentiation from the other typhus fevers often remains impossible till the characteristic *Proteus OXK* reaction becomes positive.

Differential Diagnosis. The diagnostic features shown in the table dealing with the differential diagnosis of the fevers of the typhus group should be consulted (*see* p. 185).

Prognosis. Now that effective treatment with the newer antibiotics is available death or prolonged disablement need rarely occur except among old or previously debilitated patients. Unfavourable features are the same as in louse typhus.

Treatment. Chloromycetin (chloramphenicol) has been found remarkably effective ; probably aureomycin and terramycin would be equally so but they have not been much used. Chloromycetin, given by the mouth, in initial doses of 2·0–3·0 gm. followed by doses of 0·25–0·5 gm. every four to six hours causes a rapid fall in the temperature and improvement in the condition of the patient. The drug is expensive so that it may have to be sparingly used, but even if only small quantities are available they should be given in every case in which there is danger to life.

When, as usually happens, the treatment is started after the sixth or seventh day of the fever there is no further rise of temperature, but if the first dose is given before the end of the fifth day there is often a recrudescence of the fever. Smadel found that this occurred in 8 out of 10 patients within five to sixteen days after the temperature had fallen to normal as the result of treatment with 3·4–4·0 gm., starting on the average 3·1 days after the onset. Obviously all the rickettsiæ had not been destroyed and the patients had not yet acquired enough immunity to prevent the multiplication of the surviving organisms. The relapses responded readily to a further short course of treatment but convalescence was actually delayed by giving the drug so early in the illness. The ideal dosage has still to be determined, but in the meantime the choice seems to lie between delaying treatment till six days after the onset, unless the patient's condition causes anxiety, and starting the treatment as soon as the diagnosis is made, even on the second or third day. If the latter plan is adopted a further course of treatment will be given for the relapse, or the original treatment can be followed by giving suppressive doses of 1·0–2·0 gm. every two or three days for about a fortnight.

Nausea and vomiting are not infrequent during the treatment ; these are seldom so severe as to make it necessary to withhold the drug ; they are less troublesome if milk is given with each dose. An

important point is that large doses of chloromycetin and the other antibiotics given by the mouth for long periods of time may cause riboflavin deficiency by their adverse action on the intestinal flora; the diet should therefore contain ample supplies of vitamins of the B group.

The general lines of treatment are on the lines suitable for cases of louse typhus. Important points are that seriously ill patients must never be sent on long and fatiguing journeys to hospital and that exertion must be avoided for a month or more after severe attacks.

On the other hand much harm can be done by suggesting to the patient that his heart is likely to be permanently damaged. Many patients became demoralised during the war with Japan by the alarmist attitude of the doctors and attendants.

Prevention. The short-term measures of prevention are avoidance or destruction of the larval mites in localities in which infection exists. The long-term policy includes also the destruction of the rodent reservoirs of infection.

For the reason already given destruction of the rodents may add to the danger of infection unless it is possible to deal at the same time with the already infected larval mites. For personal protection the wearing of mite-proof clothing impregnated with dimethyl (or dibutyl) phthalate is essential, and even when protected in this way care should be taken to avoid sitting, lying or standing still in places infested by the mites. Burning the grass and vegetation, preferably after spraying with inflammable oil, is a useful measure in mite-infested areas. Long-term measures can then be applied if the area is needed for planting or cultivation; these consist in clearing the land of grass and low vegetation, rat destruction and depriving the rats of food supplies.

If possible the clearing work should be by machines and by persons who have already had attacks of the disease.

SPECIAL FORMS OF MITE TYPHUS

Now that all the varieties of mite-borne typhus fever are known to be caused by strains of *R. tsutsugamushi* of varying virulence there is no need to employ such names as Rural Tropical Typhus, Mite Fever of Sumatra, Indian XK Typhus, etc. The choice of a name lies between mite typhus, tsutsugamushi disease, and scrub typhus. The first of these is now widely accepted as the most suitable, but if a name with an international flavour is desired the disease could be called "Trombiculid Typhus." The name of the country in which the disease occurs can be added, for example mite typhus in India.

Differential Diagnosis of Fevers of the Typhus Group

Success in the differential diagnosis of the typhus fevers depends first of all on suspicion of the existence of these fevers in the locality and it should be assumed that there are few places in the tropics in which one or more fevers of the group do not occur. In every case of

DIFFERENTIAL-DIAGNOSTIC FEATURES OF THE FEVERS OF THE TYPHUS GROUP

	Louse typhus	Flea typhus	Tick typhus	Mite typhus
Epidemiological type	Demic.	*Zootic.*	*Zootic.*	Zootic.
Transmission to man.	Man—louse—man.	Rat—flea—man.	Lower vertebrate—tick—man.	Rodent—mite—mite—man.
Incidence	Epidemic or endemic.	Sporadic.	Sporadic or small outbreaks.	Sporadic or local outbreaks.
Distribution, geographic and climatic.	Cosmopolitan, *rare in* continuously hot climates.	*Cosmopolitan in hot or warm* regions.	*Foci in every continent in* season of tick activity.	Foci only in Oriental countries, in damp soils covered with grass or scrub.
Other conditions associated with prevalence.	*Louse infestation,* bad hygiene, movements of population.	Rat and *Xenopsylla infesta*tion.	*Tick infestation.*	*Trombiculid mite infestation.*
Localities affected	Not localised.	A place disease of rat-infested buildings.	A place disease.	A place disease of grass-grown or scrub land.
Severity	Usually severe.	Seldom severe.	Very variable.	Very variable.
Primary lesion	None.	None.	Rare except in certain types.	Common in some types, rare in others.
Lymphadenitis	None.	None.	*Local* when "*tache noire*" occurs.	*Generalised is usual.*
Rash:—				
Visibility	Moderate.	Slight.	Usually conspicuous.	Slight to moderate.
Petechiæ	*Usual.*	*Rare.*	*Usual in severe cases.*	*Rare.*
Distribution	First on trunk; less on limbs, seldom on face, palms and soles.	As in louse typhus.	First on limbs, then generalised; often on face, palms and soles.	Chiefly on trunk; seldom on face, hands or soles.
Duration	*Variable, up to 10 days.*	*Short.*	*Often prolonged.*	*Usually 7 to 10 days.*
Persistent staining	Slight.	Little or none.	Pronounced in most cases.	Not pronounced.
Type of *Proteus OX* reaction.	*OX*19, high titre.	*OX*19, high titre.	Variable; *OX*2 or *OX*19, the latter in lower titres *than in louse typhus, or* indeterminate.	Nearly always of *OXK* type.
Type of complement-fixation reaction.	Positive with *R. prowazeki* in higher titre than with *R. mooseri.*	Positive with *R. mooseri* in higher titre than with *R. prowazeki.*	Positive with *R. rickettsi* antigen.	Positive with *R. tsutsugamushi* antigen of suitable strain.

continued or remittent fever which lasts more than seven days and in which the cause cannot be found by careful clinical examination a Weil-Felix test with the three types of *Proteus OX* bacilli should be carried out and repeated at weekly intervals. In all the fevers of the group a rising-titre agglutination with one or more of these types nearly always occurs, and is strong evidence that the disease belongs to the group. The type of the reaction sometimes points to the correct diagnosis ; for example an *OXK* reaction in the geographical area of occurrence of mite typhus is almost diagnostic. An *OX*2 reaction favours the diagnosis of tick typhus but may occur also in louse typhus and flea typhus. An *OX*19 reaction is usually found in louse typhus and flea typhus and often in tick typhus.

A general survey of the clinical features, the known prevalence of the disease in the area, the evidence pointing to recent bites by one or other of the known vectors, and the climatic conditions prevailing at the time will usually provide useful clues to the diagnosis.

There will remain some cases in which a reliable diagnosis cannot be made without the help of complement-fixation or rickettsia-agglutination tests, and unfortunately these demand the services of highly skilled experts and special laboratories.

The most important practical point is to detect louse typhus when it occurs, but this disease is not common in the tropics except in places where high altitude provides cool or cold weather conditions for part of the year. If louse-infestation occurs in the patient or his associates the safe rule is to carry out disinfestation even if lice are not believed to be concerned in transmission.

The table shows the chief factors bearing on the differential diagnosis ; all of these must be taken into account so as to provide cumulative evidence pointing to the vector concerned.

When there is only a suspicion of the occurrence of a fever of the typhus group treatment with chloromycetin or aureomycin should be given in severe attacks ; these drugs have a wide range of efficacy and are valuable in many other fevers liable to be mistaken in the early stages for rickettsial fevers, for example typhoid fever, relapsing fever and other spirochætal fevers, brucellosis and other bacterial infections.

The possible occurrence of malaria as a complication should always be borne in mind, especially in cases which do not respond to treatment with the antibiotics.

OTHER RICKETTSIAL FEVERS

For reasons already stated it is considered suitable to regard the other three rickettsial fevers as independent diseases rather than as belonging to the typhus group. These fevers are trench fever, Q fever and rickettsialpox ; their chief ætiological and epidemiological features are listed in the Table on p. 153 to which reference should be made. Each will be briefly described.

DIFFERENTIAL-DIAGNOSTIC FEATURES OF THE FEVERS OF THE TYPHUS GROUP

	Louse typhus	Flea typhus	Tick typhus	Mite typhus
Epidemiological type	Demic.	Zootic.	Zootic.	Zootic.
Transmission to man.	Man—louse—man.	Rat—flea—man.	Lower vertebrate—tick—man.	Rodent—mite—mite—man.
Incidence	Epidemic or endemic.	Sporadic.	Sporadic or small outbreaks.	Sporadic or local outbreaks.
Distribution, geographic and climatic.	Cosmopolitan, rare in continuously hot climates.	Cosmopolitan in hot or warm regions.	Foci in every continent in season of tick activity.	Foci only in Oriental countries, in damp soils covered with grass or scrub.
Other conditions associated with prevalence.	Louse infestation, bad hygiene, movements of *population*.	Rat and *Xenopsylla* infestation.	Tick infestation.	*Trombiculid* mite infestation.
Localities affected	Not localised.	A place disease of rat-infested buildings.	A place disease.	A place disease of grass-grown or scrub land.
Severity	Usually severe.	Seldom severe.	Very variable.	Very variable.
Primary lesion	None.	None.	*Rare except in certain types.*	*Common in some types, rare* in others.
Lymphadenitis	None.	None.	Local when "*tache noire*" occurs.	Generalised is usual.
Rash:—				
Visibility	Moderate.	Slight.	Usually conspicuous.	Slight to moderate.
Petechiæ	Usual.	Rare.	Usual in severe cases.	Rare.
Distribution	First on trunk; less on limbs, seldom on face, palms and soles.	As in louse typhus.	First on limbs, then generalised; often on face, palms and soles.	Chiefly on trunk; seldom on face, hands or soles.
Duration	Variable, up to 10 days.	Short.	Often prolonged.	Usually 7 to 10 days.
Persistent staining	Slight.	Little or none.	Pronounced in most cases.	Not pronounced.
Type of *Proteus OX* reaction.	*OX*19, high titre.	*OX*19, high titre.	Variable; *OX*2 or *OX*19, the latter in lower titres than in louse typhus, or indeterminate.	Nearly always of *OXK* type.
Type of complement-fixation reaction.	Positive with *R. prowazeki* in higher titre than with *R. mooseri*.	Positive with *R. mooseri* in higher titre than with *R. prowazeki*.	Positive with *R. rickettsi* antigen.	Positive with *R. tsutsugamushi* antigen of suitable strain.

and (6) the afebrile type in which recurring spells of pain, sometimes accompanied by diarrhœa, are the only symptoms.

The pronounced tendency to recurrence of pains and fever is the most characteristic feature of the disease; even in the so-called afebrile attacks the temperature will usually be found slightly raised if it is taken hourly during the paroxysms of pain.

Special Features. The pains are the most prominent symptoms, they are often very severe, especially when the patient is lying down in a warm bed. They may be referred to any part of the trunk or extremities, but are usually most severe in the tibial region and are called "shin-bone pains."

A moderate degree of polymorphonuclear leucocytosis is usual. A rash consisting of red macules which appear for a short period during the spells of fever has been observed in a few cases. The Weil-Felix reaction is rarely positive; high-titre agglutination of *Proteus OX*19 indicates a co-existing or recent infection with louse typhus.

Diagnosis. No laboratory test is yet available so that the diagnosis is based on the clinical and epidemiological features and on the exclusion of such diseases as malaria, typhus fever, influenza, cerebrospinal fever, dengue, relapsing fever, leptospiral fevers, chronic rheumatism and rheumatic fever. In the presence of an epidemic there is seldom any difficulty, though in some outbreaks large numbers of cases have occurred before the disease was recognised.

Prognosis. There have been no deaths among previously healthy patients, but convalescence is sometimes prolonged.

Treatment. The newer antibiotics can be expected to be effective; they have not yet been tried. Lumbar puncture has been found helpful when the headache is unbearable.

Prevention. This is on exactly the same lines as have been found so effective in louse typhus and louse relapsing fever. No vaccine has yet been prepared.

RICKETTSIALPOX

Definition. A zootic rickettsial fever caused by *Rickettsia akari* which is transmitted from infected house mice by a mite, *Allodermanyssus sanguineus*.

This fever was first described by Sussman in 1946; it was closely studied in the same year by a team of workers led by Smadel who called it rickettsialpox.

Between January and October, 1946, 124 cases occured among 2,000 persons living in 69 large buildings 15 miles distant from the centre of New York. Near the buildings there were plots of neglected grass and scrub land. Smaller outbreaks occurred in four of the five boroughs of New York. Infected mice were found in every house in which cases occurred. Outside New York only one case has yet been reported—from Boston.

TRENCH FEVER

Synonyms. Volhynian fever, five-day fever.

Definition. A fever caused by *Rickettsia quintana* (*R. volhynica*) which is transmitted from man to man by human lice.

Trench fever resembles louse typhus in being a rickettsial disease and in being transmitted in the same way, but it differs sharply in its clinical features, and in the almost complete absence of fatal attacks.

The disease was quite unknown till the 1914–18 war, when it suddenly became prominent on both fronts. Byam estimates that there were about 800,000 cases in the Allied Forces on the Western Front. Shortly after the end of the war the disease disappeared and nothing was heard of it except for a small laboratory outbreak in Poland and a few minor outbreaks in Galicia and Japan. The disease must have persisted in unrecognised form in Eastern Europe, because among the German troops on the Eastern Front, thousands of cases occurred in the second world war.

Trench fever is of great potential importance as a war disease owing to the great wastage of manpower that may result from the prolonged incapacitation caused by severe attacks.

Ætiology. The rickettsiæ multiply rapidly in infected lice and are transmitted by the fæces of the insects in the same way as *Rickettsia prowazeki*. Heavy louse infestation and close contact between infected and non-infected persons are necessary for the continued transmission of infection. The blood of patients is infective to lice throughout the illness, and sometimes for weeks, months, or even years afterwards.

Symptoms. After an incubation period which ranges from six to twenty-five days, there is a sudden onset with a rapidly rising temperature, headache, severe pains in the back and limbs, and usually conjunctival congestion. The course of the illness is extremely variable; some of the chief types are : (1) the " typical form " which is highly characteristic ; there are short, sharp paroxysms of fever with chills ; these recur every four to six days and are accompanied by severe pains in various parts of the body, but especially in the tibial region. Between the paroxysms the patient is relatively comfortable. The total duration of the illness may be ten days to two months or more. Some recent outbreaks among German troops have been reported to be of a mild type with less than four spells of fever in most of the cases ; (2) the undulant type in which there are short waves of fever, each lasting two or three days, and recurring with the same periodicity as in the typical attacks ; (3) the short-fever type in which there is only one spell of fever lasting from two to seven days, and hardly distinguishable from uncomplicated influenza ; (4) an initial spell of fever like that of type (3) may be followed by recurring spells as in types (1) and (2) ; (5) the irregular-fever type in which paroxysms or short waves of fever occur indiscriminately and at irregular intervals ;

so that infection would soon die out if it were confined to human beings.

The disease was discovered in 1935, and described in 1937, by Derrick who detected cases among workers in slaughter houses in Brisbane. In 1937 Burnet and Freeman discovered the rickettsia which was afterwards called *Rickettsia burneti.* In 1939 Derrick, *et al.* isolated the rickettsiæ from certain ticks and from the bandicoot rats on which the ticks fed. In 1939 Dyer in the U.S.A. showed that a filter-passing virus discovered in a tick by Davis and Cox in Montana was immunologically identical with *Rickettsia burneti* and that a case of laboratory infection with the Montana "virus" was very similar to the descriptions of Q fever.

Between 1941 and 1945 many cases were occurring among German troops and the civilian population in the Balkans where the disease was diagnosed as "Balkan grippe." A strain of infection isolated in 1944 by Caminopteros in Greece from a patient was later identified as *R. burneti.*

In 1945 numerous outbreaks occurred among British and American troops in the Mediterranean area, especially in Italy ; these were diagnosed as atypical pneumonia, but were soon found by American workers to be Q fever.

Since 1945 the disease has been found to occur frequently in the U.S.A. especially in California and Texas, in Switzerland, Germany and Greece. Almost all the countries of Europe, including England, and of Africa are known to be infected so that the disease may have a world-wide distribution.

Many laboratory outbreaks have occurred, apparently caused by droplet or dust air-borne infection resulting from the processing of yolk-sac suspensions containing the rickettsiæ.

Transmission to Man. In natural conditions this is usually from infected cattle, sheep, goats or camels. Signs of illness in these or other infected animals are seldom seen. Drinking infected milk, handling the carcasses or hides of infected animals and contact with living animals are the conditions most favourable to human infection. Rickettsiæ when dried remain viable for long periods so that the handling of dried hides, hair or wool and the inhalation of dust from places occupied by infected animals can cause infection. Patients sometimes disseminate infected droplets into the air and so may infect persons occupying the same room.

Clinical Features. The disease varies greatly in severity, duration and symptomatology. Very mild or even subclinical attacks lasting a day or two have been revealed by retrospective serological tests ; most of the cases last two to seven days and are mild to moderate in their severity but prolonged severe attacks may occur and these are sometimes fatal in old or debilitated patients. The incubation period ranges from about ten to thirty days but is usually fifteen to twenty days.

Rickettsiæ were isolated from patients, mice and mites by intraperitoneal inoculation of mice. The appearance and cultural characters of the rickettsiæ were like those of the organisms of the other rickettsial fevers.

The chief clinical features were :—an initial lesion like the eschar of mite typhus was detected in 95 per cent. of the cases ; a few days later there was an attack of remittent fever which lasted one to ten days. A maculopapular rash appeared on the first to the fourth day. In the centre of each spot a vesicle soon developed ; this dried up leaving a small scab. The rash lasted four to seven days. There were no deaths.

A very remarkable feature of the disease is that the complement-fixation test in many of the cases gives exactly the same reaction as occurs in Rocky Mountain spotted fever though the two diseases are quite different in their clinical and epidemiological aspects and in their Weil-Felix reactions which are usually positive in Rocky Mountain fever and negative in rickettsialpox. No satisfactory explanation has yet been given of this paradoxical finding which suggests that the complement fixing antigens cannot always be regarded as an infallible indication of the nature of the diseases in which they occur. In rickettsialpox a negative agglutination response with a non-specific organism, *Proteus OX*19, is of greater value in differential diagnosis than a positive complement-fixation response with the causative rickettsiæ. In this connection it may be noted that in mite typhus the "non-specific" Weil-Felix reaction with *Proteus OXK* is more useful than the "specific" complement-fixation test with *R. tsutsugamushi* which gives conflicting responses with different strains of the organism.

Rickettsialpox deserves attention as showing the possibility that other new rickettsial diseases may occur in places where they have not yet been recognised.

Q FEVER

This disease was originally called by the letter Q, an abbreviation of the word query, to indicate that it was a problem disease of questionable ætiology. It is often wrongly assumed that Q is an abbreviation of Queensland where the disease was discovered.

Definition. A primarily zootic fever caused by *Rickettsia* (*Coxiella*) *burneti* which is transmitted to man from various lower vertebrates, chiefly cattle, sheep and goats. Although transmission among lower animals is often by various ticks it may also be by direct contact, and transmission to man is mostly by contact, rarely by ticks, which, however, may perhaps be essential for maintaining the pathogenicity of the rickettsiæ among the animals, and so, indirectly, for maintaining the disease among human beings. Infection is occasionally transmitted from man to man by contact, but rarely for more than a single passage

CHAPTER IX

BACTERIAL DISEASES OF RODENTS COMMUNICABLE TO MAN—PLAGUE, TULARÆMIA AND MELIOIDOSIS

I. PLAGUE

THE name "plague" used to be applied to any kind of fatal epidemic disease, but it is now restricted to the disease which is caused by the plague bacillus.

Definition. Plague is a disease which is caused by the plague bacillus (*Pasteurella pestis*). The commonest form of the disease is a severe septicæmia accompanied by the appearance of inflamed lymphatic glands: this form is called bubonic plague, or *Pestis bubonica*. When the septicæmia is so acute that death occurs before the appearance of buboes the name "septicæmic plague" is applied, and when the disease is conveyed by droplet infection, so that a fatal primary pneumonia is produced, it is called "pneumonic plague." The latter form will be described separately, as its symptoms and mode of spread are quite different from those of the common bubonic plague (*see* Fig. 39).

History. The disease is one of great antiquity; there are references in the Bible and in some ancient Hindu books to outbreaks which may have been plague. During historical times there have been great pandemics at varying intervals; these have spread all over the part of the world which was known at the time; some of them have wiped out 10–20 per cent. or more of the population of the globe. Thus the outbreak of 1348 is believed to have carried off one-fourth of the population of Europe; and that of 1664–65 destroyed 70,000 persons, or one-seventh of the inhabitants of London. Since then no serious outbreaks have occurred in Great Britain, though a few cases have been met with in our ports and in Suffolk during the last pandemic. This broke out in Hong Kong in 1894 from an old endemic centre in the Yunnan province of south-west China, was carried by sea to Bombay, and has since spread over most of the world. In 1894 Yersin first found the causative organism, formerly called *Bacillus pestis* but now known as *Pasteurella pestis*. The organism described by Kitasato was Gram-positive and motile, and differed from the plague bacillus in other respects. Ogata, with the consent of Kitasato, reported to the Government of Japan that plague at Kobe was caused by the bacillus of Yersin and not by that of Kitasato. The name of Yersin, rather than that of Kitasato, ought to be associated with the bacillus.

The close relationship between a fatal epizootic disease in rats and plague in man has been known for centuries, but it was only during the last pandemic that the ætiology of plague was worked out. As early as 1898 Simond, in Bombay, produced plague in mice by injecting

The onset is sudden or gradual, usually with severe headache, chills, sweating and body pains.

During the attack there is often a cough, sometimes with expectoration, and meningismus occasionally occurs. Pharyngeal injection is common ; in some cases crepitant or moist râles can be heard over certain areas in which dullness on percussion can occasionally be detected. X-ray examination often reveals one or more areas of infiltration of the lungs ; these are most frequent in the middle and lower zones and at the roots of the lungs. Leucocytosis is rare ; leucopenia is common. The pulse tends to be relatively slow.

The pathognomonic feature is the occurrence of a rising-titre reaction with the complement-fixation test, but a significant titre of 1–10 or over may not be reached till the end of the second or third week. The reaction remains positive for several months and so a retrospective diagnosis can often be made. When suitable suspensions of *R. burneti* become generally available the rickettsia-agglutination test will probably be widely used in diagnosis.

The Weil-Felix test is nearly always negative and so is not helpful in diagnosis, except by excluding fevers of the typhus group.

Treatment. Aureomycin has been tried and has been considered helpful, but some cases have failed to respond to large doses given over a long period. This drug and chloromycetin are worth trying in severe cases but they are hardly needed in mild attacks.

Prevention. Personal protection of laboratory workers and other persons exposed to special risk is afforded by yolk-sac vaccines. Milk is made safe by heating to nearly boiling point. The rickettsiæ survive in yolk-sac suspensions heated to 63° C. for forty minutes and so are more resistant to heat than the rickettsiæ of the typhus fevers.

Elimination of infection among flocks and herds is not considered practicable at present.

J. W. D. MEGAW

pointed out in 1917 that, in addition to the effect of a high temperature in reducing plague, a very dry atmosphere, as indicated by a high saturation deficiency, rapidly brings an epidemic to a close, even with a temperature below 80° F., but with a low saturation deficiency below 0·300 plague may even increase when the mean temperature is over 80° F. He defined saturation deficiency as "the difference between the actual tension of aqueous vapour present in the atmosphere at the temperature in question, and the tension of aqueous vapour that would be present in a saturated atmosphere at the same temperature." The saturation deficiency is thus a measure of the drying capacity of the air, a high degree of which is inimical to the life of fleas. The writer later studied the meteorological data for three decades in various parts of India in relation to the prevalence of plague, and confirmed and extended Brooks' observations. The decline of plague everywhere in India during the height of the hot season is due to high temperatures and saturation deficiencies. The early increase of plague in the monsoon months in the Central Provinces and Bombay Deccan is due to the comparatively low temperatures and saturation deficiencies which occur at that season, as compared with the North-West of India, where there is no appreciable increase of plague until November and December. Moreover, the variations from the mean of the temperatures and of the saturation deficiencies explain most of the yearly variations of plague incidence in Northern India from year to year, and their study may facilitate forecasts of the probable rise or fall of plague incidence. In Madras, King found that a weak monsoon, with comparatively high temperature and low humidity, prevented the disease from being carried over from one plague season to the next. In Java, with a fairly uniform temperature, plague prevails at all seasons. The observed tendency of plague to persist endemically for long periods in the Himalayas, and the mountains of Java and Madagascar, after an epidemic has subsided in the adjacent lowlands, may also be explained by the comparatively low temperatures and saturation deficiencies in tropical mountains. In Madagascar F. Estrade found that *X. cheopis* survived longest at a temperature of 15°–20° C. (59°–68° F.) and with a relative humidity of 85–95 per cent. In Russia it has been shown that fleas may survive in the nests of susliks in an infective condition for seven months, and could thus carry the infection over the non-epizootic period. P. A. Buxton found that very high humidities produced moulds which killed female fleas.

Cimex lectularius, the bed-bug, has also been reported to retain plague bacilli up to 147 days after being fed on infected rats, and in one case the bite of an infected bug transmitted the disease in Russia. A tick, *Argas persicus*, has also retained living plague bacilli up to 110 days.

Ætiology. *Pasteurella pestis* is a short, thick, non-motile bacillus from 1μ to 2μ in length. It stains more deeply at each end than

them with extracts of crushed fleas from a plague rat. A little later Ashburton Thompson supported the rat-flea theory of infection on epidemiological grounds in Sydney; and in 1902 Gauthier and Raybaud, in Marseilles, succeeded in infecting rats through rat-fleas. In 1905 Glen Liston, working in the Bombay Plague Laboratory, recorded important observations in support of the rat-flea theory; these were confirmed and extended by the Plague Investigation Committee under C. J. Martin during 1907–16, which established the theory with important practical results.

Geographical Distribution. Plague spread from Hong Kong to Bombay and Egypt in 1896, and was carried to Japan about the same time. In 1899 the Philippines and South America became infected, but the disease did not gain a footing in the East Indian Islands and in Ceylon until much later, because the climatic conditions, docking facilities and the local rat-flea fauna were less favourable for its spread. India has suffered most severely from plague, with over 10 million deaths in twenty years; nearly one and a half million of these occurred in 1907, when the epidemic reached its height in India. It sub sequently declined to such an extent that only 116,792 plague deaths were recorded in British India during 1935–39, since when it has continued to decline.

The countries in which the disease has been prevalent include Manchuria and Eastern Siberia, which have been affected by the deadly pneumonic form, China, Indo-China, the East Indian Islands, Java, Thailand, India, Burma, Ceylon occasionally, Iraq, Aden and other parts of South-West Asia, Northern Africa and Nigeria, Uganda, Kenya, East Belgian Congo, Madagascar and Southern Africa, Sydney occasionally, California to a slight degree with infection of squirrels, and parts of South America (Peru, Chile, Ecuador, Argentina and Brazil), to which it has been carried by sea, through rats and their fleas.

Sylvatic or Rural Plague differs from the rat-borne city epidemics in giving rise to sporadic cases scattered over extensive country areas through epizootic infections of a number of animals. These include the Californian ground squirrel, the South African gerbille and multi-mammate mouse and rat, the marmots of Russia and Manchuria, chipmunks, a cotton-tail rabbit in America, wood and kangaroo rats, etc. The countries in which sylvatic plague has been widespread include Canada, the Western U.S.A., Mexico, most of the countries of South America down to Argentina, as well as East Africa, and the Belgian Congo down to South Africa. In some South American countries it has died down for unexplained reasons. Although serious human epidemics do not arise, the infection among these widely scattered animals is very difficult to eradicate.

Epidemiology. The seasonal incidence of plague in India varies in different provinces in accordance with the temperature and humidity. R. St. John Brooks, when working with the Indian Plague Commission,

contract plague if kept in cages in plague infected houses, and so have been used as danger signals. If one of these animals dies during plague prevalence the house should be evacuated.

The rats most affected by plague outbreaks are the grey rats, *Rattus norvegicus*, found chiefly in drains and grain stores, and the smaller black rat, *Rattus rattus*, the latter being found most frequently in houses. Very extensive Bombay investigations showed that the maximum seasonal incidence of plague occurred in the grey rats slightly before that in the black rats, and the height of the curve in man followed two weeks after the maximum in the black rats, which are most closely associated with the outbreaks. In Tunis E. Gobert found the domestic rat, *R. alexandrinus*, to be the chief danger and to have been present at least since the time of the Crusades. In South Russia the suslik, or ground squirrel, is an important carrier.

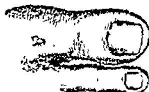
The role of the rat-flea in transmitting plague from one rat to another was established by the Indian Plague Commission by experiments carried out in Bombay in rat-proof compartments. When all the fleas were removed by chloroforming the rats and combing out all their fleas, healthy rats never contracted plague from the most intimate contact with plague-infected rats. Further, healthy rats did not get plague even if they were kept in close proximity to plague rats, provided they were protected from the fleas of the diseased rats by being enclosed in cages made of fine wire gauze.

The disease is carried from one rat to another by the bites of rat-fleas which have become infected by sucking the blood of a rat suffering from septicæmiac plague. Rats dying of plague in nature never show any primary infection of the mesenteric glands so that obviously the disease is not transmitted by the digestive system. Guinea-pigs develop cervical buboes, because these animals cannot free themselves from the fleas on their necks.

The rat-flea, which is chiefly responsible for the transmission of plague in the tropics, is the *Xenopsylla cheopis*, but in colder climates *Ceratophyllus fasciatus* is believed to be capable of transmitting the disease. It was shown by L. E. Hirst that the common rat-flea of Madras, Ceylon and the Malay States, *Xenopsylla astia*, is a far less efficient carrier of plague infection than *X. cheopis*. He suggested that this is an important factor in explaining the distribution of plague in India, and his views have been confirmed in Madras, where *X. astia* has been found to be a poor carrier of plague and has produced few and small outbreaks which do not persist through the off-season. It has also been noticed that the more dangerous *X. cheopis* was liable to be introduced in cotton and to flourish in humid cotton mills, and Thornton has pointed out that plague in Uganda has been mainly associated with the cotton industry. Fleas have also been suspected of having been able to survive in jute imported to South America from India.

at the centre, producing a bi-polar appearance, and it is Gram-negative. No spores are found, so that it is readily killed by heating to 60° C., by exposure to strong sunlight for a few hours, and by drying for several days ; it can resist freezing for many days. It grows easily





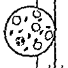


FIG. 39. Story of an attack of plague.

in ordinary culture media ; in broth on which fat is floating it forms stalactite-like growths, best seen by lighting a candle behind the flask in the incubator.

Animals susceptible to inoculation with plague include in addition to those already mentioned, mice, guinea-pigs and monkeys, but bovines, pigs and birds are immune. Guinea-pigs very readily

flooded during the monsoon ; there is also the low incidence of 0·015 per mille in Western Bengal, where the houses are scattered, thin-walled huts, in which few rats are found. On the other hand, the incidence rises rapidly to 2·89 per mille in the neighbouring area of Western Bihar, where the people live in closely aggregated thick mud-walled huts, with many rats which are also heavily infested with fleas. In Egypt the conclusion was reached that nothing short of the demolition of the mud-houses, and the construction of rat-proof ones, would keep away plague. In cities brick rat-proof houses are comparatively free from plague ; on the other hand, grain store-houses, with numerous rats, are especially liable to become plague centres.

The spread of plague from one place to another is usually by the agency of human beings who travel during the incubation period of the disease. After the infected person is attacked no new cases arise directly from him, but after an interval of about two weeks rats begin to die of plague, through infection by fleas which had bitten the first patient ; next plague cases begin to appear in those living in the house, and the disease then may spread through the village. Migration of rats during the incubation period may also carry plague for short distances. Rats and their fleas may also carry the infection in grain, and infected rats on ships are the most common source of infection of new countries by sea. The disease usually appears first in the neighbourhood of the docks, being carried by infected rats which have escaped from the ships to the shore. Human beings were also said by the Indian Plague Commission to be able to carry infection from place to place through rat-fleas, which might be conveyed in their baggage or on their persons, even though the human hosts themselves remained free from the disease. Infected fleas may also be conveyed in bales of cotton, jute or other merchandise, but the fleas are not considered to be capable of surviving for more than a few days when the air temperature is high. Apart from the pneumonic form, plague in man is very rarely directly infectious from one person to another, but it is directly inoculable, and a number of fatal cases have resulted from cuts or scratches at post-mortems, or even while dissecting bodies of persons who have recently died of plague, as occurred to some medical students in Calcutta. Insanitary conditions, apart from *favouring the multiplication of rats, play no part in the epidemiology* of bubonic plague. The development of immunity in the rat population of an infected village or town is an important factor in limiting the duration of the outbreak. Thus S. S. Sokhey and G. D. Chitre in India found the susceptibility of rats to inoculated plague varied from 0 to 93 per cent. in different cities ; it was in inverse proportion to the incidence of plague. Tests in mice showed no hereditary immunity, so these observers think that in the presence of plague susceptible races of rats die out, leaving naturally immune ones.

The Indian Plague Commission showed that the *P. pestis* multiplies up to forty-five days in the gastro-intestinal canals of fleas, and that in some of the insects the bacilli grow back into the œsophagus in such numbers that they block it, as found by C. J. Martin and Bacot, so that when the flea again attempts to suck blood the organisms are regurgitated and cause infection. Previously it had been thought that the excreta of the flea, containing plague bacilli, were deposited on the skin when the insect was feeding, and were rubbed into the minute wound produced by the bite of the insect. Fleas diminish greatly in numbers when the mean temperature rises to over 85° F., and the "blocked" fleas are the first to die, as they are unable to suck blood properly. In this way the rapid fall of plague in the hot dry season is readily explained.

The infection of man occurs when rats die of plague in a house, for as the body of the rat cools the rat-fleas leave it, and they will then bite man for want of a more acceptable victim. They usually bite the bare feet or the legs, and so the buboes are commonly situated in the inguinal region. It is of interest to note that in India and elsewhere sweepers, who pick up dead rats, often develop axillary buboes, as the rat-fleas hop on to their hands and arms from the bodies of the rats that are still warm ; but cold, dead rats are much less dangerous to handle, as the fleas will have already deserted them.

In a small outbreak of plague in Suffolk in England, Letham suggested that human fleas were probably the carriers as rat infection was rare. In Java H. V. Hoesen found that in a densely populated flea nursery, to which fresh rats were added as the old ones died, the fleas continued to infect the rats for from twenty-nine to thirty-three days. In a village near Bombay the inhabitants were all removed as soon as one case of plague had occurred ; guinea-pigs were then placed in the houses, and it was found that these continued to be infected for two months through the rat-fleas. No less than 45 per cent. of the houses were proved to have become infected by the rats. The importance of prolonged evacuation of infected houses by man is thus evident, so also is the uselessness of ordinary disinfection of houses with mud walls and floors, as the rats are not destroyed. The disease may be carried over from one season to the next through persistence of the disease in the rats, which occasionally suffer from a non-fatal chronic form of plague. In these rats abscesses are sometimes found which contain the *P. pestis.* In the Punjab Browning-Smith found over 50 per cent. of the village outbreaks to be recrudescences, which were brought about in this way without the re-importation of the disease.

Housing conditions greatly influence the incidence of plague, which varies directly with the capacity of the house for harbouring rats. This is strikingly illustrated by the remarkably low incidence of under 0·01 per mille in Eastern Bengal and Assam, which are low-lying and

with 5 drachms of mustard oil or castor oil to make a paste, then 1 drachm of red pepper and a handful of crushed dried neem leaves are added. The whole mixture is placed in a rat-hole over a 9-inch wick of cloth which has been soaked in a saturated solution of potassium chlorate and then dried, the wick is ignited and the holes closed. As rats soon learn to avoid any particular poison a change of plan should be made frequently. Just before the plague season a general house-cleaning aids in reducing the number of rats which are harboured. Rat virus for producing epidemics in these animals has not proved to be of much value.

Fumigation is employed to kill rats and their fleas on ships to prevent the carriage of plague from one place to another. The safest method is to burn sulphur dioxide in iron vessels placed over tubs of water in sealed holds and cabins ; 2 lb. of roll sulphur should be used for every 1,000 cubic feet of space. Hydrocyanic gas is still more potent when used by experts, but is dangerous, and has caused a number of human deaths. George and Webster have reported promising results in reducing plague in infected villages by fumigating thousands of rat burrows in the houses with " cyanogas," which is said to contain about 50 per cent. of calcium cyanide. In Bechuanaland M. Gerber recorded that the disinfestation of rats and grain in connection with 39,186 huts was followed by the practical cessation of plague. In the Bombay Research Laboratories S. S. Sokhey found that " calcid," containing only twice the amount of hydrocyanic gas contained in " cyanogas," was forty-two times as effective. For the fumigation of ships, which has done so much to limit the spread of plague over the world, hydrocyanic acid is mostly employed in preference to sulphur under careful control in the proportion of 2 oz. per 1,000 cubic feet of space. Carbon monoxide and carbon dioxide gas are also used, but they often fail to kill the dangerous rat-fleas. Similar measures can be used for disinfesting articles which can be sealed up for effective fumigation. In California it has been found that liquid methyl bromide has a high lethal action on rats and fleas next to that of hydrocyanic acid, and it has the great advantage of not being toxic to food. About 10 c.c. are required for each burrow. In South Russia, I. J. Taut was successful in destroying the susliks, and in thus preventing human plague, by treating their burrows with carbon bisulphide and chlorine, and then plugging them. In parts of Basutoland the gerbille carriers of plague infection were practically wiped out by baiting all their burrows with poisoned wheat, and plague was thus prevented.

Dusting the burrows and runs of rats with a 10 per cent. D.D.T. powder and spraying the rooms with D.D.T. solutions or suspensions, as described in the prevention of malaria, will quickly destroy the rat fleas.

The evacuation of houses is the most essential measure once plague has broken out. This plan has long been known to indigenous races in

Prophylaxis. As treatment plays little part in the prophylaxis against plague this subject can best be dealt with before going on to the clinical description of the disease. As with other insect-borne diseases, the chain of infection through the rats and other rodents and their fleas may be broken at any link with success ; so that destruction of the rats and their fleas, the rat-proofing of dwelling-houses and granaries, the prevention of rats from leaving ships to infect new places, and the evacuation of houses infected with plague rats may all be effective measures for controlling the disease. Inspection of passengers and crews from infected ports and isolation for seven to ten days of any persons suspected of having plague is of value.

Rat-proofing of houses is the most radical and permanent method of preventing plague in the infected areas. It is being adopted extensively in large seaport towns, especially in the vicinity of the docks, and is effected by the use of brick walls and concrete floors impervious to rats, and by eliminating hollow walls and ceilings. In California raising cottages eighteen inches off the ground affords protection against rats. In Java compulsory reconstruction of over a million and a half houses since 1914 has been followed by nearly complete disappearance of the disease in large areas. Where bamboos are used in making furniture and bedsteads, their hollows should be filled with concrete to prevent rats from breeding in them, and grain stores should always be made rat-proof. Open sewers should have vertical walls three feet deep to retain their rats. In Peru, flame-throwers have been used to kill rats and fleas in burrows.

Rat Destruction. This is an important measure where plague is prevalent. In Manila the extent of the infected area was first determined by trapping rats, thus ascertaining the limits of the area in which infected rats were found. Rat-catching was then started from the periphery of the area, working in towards the centre ; houses were made rat-proof in the same order from the periphery to the centre of the area, and the infection was thus stamped out. Heiser reported that spring traps had an efficiency of 7·47 against 0·97 for wire-cage traps, and 0·12 for poison bait. Traps after use should be placed in boiling water to remove all trace of smell before being re-set.

The most effective rat poisons are : (1) 1 part of white arsenic to 4 of rice ; (2) phosphorus rat-paste placed in holes cut in bananas ; and (3) 3 grains of barium carbonate mixed with 4 grains of dough—the last has the advantage of not being poisonous to man or the larger domestic animals in that dose. The baits should be laid in places inaccessible to children and domestic animals. Sodium fluoroacetate is still more lethal to fleas and rats, but it is so toxic that it should only be used by experts. In India an effective way of killing rats and the fleas in their runs is by the use of "neem-battis," made by mixing powdered potassium chlorate, 2 drachms ; potassium nitrate, 1½ drachms ; and sulphur, 2 drachms ; these are powdered and mixed

similar avirulent living plague vaccine in Madagascar obtained a plague death rate of 0·47 per mille in 46,879 inoculated against a rate of 1·68 per mille among 55,121 controls. Reactions are very mild. Thus Strong's earlier use of living vaccines in the Philippines has been confirmed. S. S. Sokhey, however, found that although agar-grown live avirulent plague vaccines afford good protection, they deteriorate rapidly on keeping, unless preserved at 0° C., when they preserve their activity for twenty months.

Personal Prophylaxis. The newer insecticide D.D.T. is of great value when applied as a 5 or 10 per cent. powder diluted with talc to underwear, puttees, hair, etc. A 5 per cent. solution in kerosene should also be sprayed on to the floors and the lower parts of the walls of houses to kill rat-fleas ; it retains its effects for two or more weeks. In Peru a small epidemic is reported to have been brought under control in a few days by these measures. Other valuable methods of personal prophylaxis include wearing boots, puttees and flea-proof clothing, or sprinkling the clothing with insecticides such as kerosene or powdered naphthalene when entering plague houses. Masks of cotton wool in muslin are necessary when dealing with plague pneumonia cases, as adopted by R. P. Strong and Teague in Manchuria.

Pathology. When the plague bacilli gain entrance through the skin at the site of the bite by an infected rat-flea they multiply and may produce a local reaction in the form of a vesicle or blister containing a pure culture of *P. pestis*, or they may cause no obvious local lesion, but pass to the nearest lymphatic glands, and set up inflammation with the development of the typical bubo. Some of them pass through the glands to enter the general circulation and cause a septicæmia. The lower the resisting powers of the tissues the less are the local reactions and *vice versâ*, so that in the mildest cases the primary skin vesicles are most often seen ; in the common intermediate form the local reaction occurs as a bubo of the lymphatic glands, and, in the severest form in patients with the lowest degree of resistance, the bacilli may also pass through the lymphatic glands without exciting enough reaction for the formation of a typical bubo ; in this case the almost invariably fatal primary septicæmic form of plague results. In severe cases in the late stages secondary broncho-pneumonia may occur ; the sputum of such patients is heavily charged with bacilli and is likely to cause pneumonic plague in attendants, who become infected by the inhalation of droplets which are coughed out by the patients.

The Bubo is the most prominent pathological lesion ; it is characterised by an extensive hæmorrhagic œdema around the enlarged glands. On cutting into the tissues over the bubo, much yellowish fluid is exuded. The glands are moderately enlarged, soft and hæmorrhagic, and contain many plague bacilli in the early stages, but after suppuration has taken place in those patients who survive long enough, the delicate plague bacilli usually disappear. In septicæmic cases there

endemic areas such as the Kumaon *region of the Himalayas*. Evacuation is regularly resorted to in Indian outbreaks, and has resulted in great saving of life. Fortunately, the main plague season is in the dry cold-weather and early hot-weather seasons, when the inhabitants of plague-affected cities and villages can leave their houses and camp out without great hardship. When infection has appeared in any group of residences these should be evacuated for a month or more, as the *epizootic among the rats is likely to last a long time. Guinea-pigs* should be placed in cages in some of the houses before allowing the people to return to them ; if the infection still persists these animals will contract the disease through being bitten by the rat-fleas. Rat-catching and poisoning should be carried on at the same time, and when the disease has broken out late in one plague season, these measures should be continued during the off-season when plague is at its lowest, *as in this way there is a good prospect of preventing the recrudescence* of the disease when the climatic conditions again become favourable to the occurrence of plague.

Inoculation is the most important method of personal prophylaxis. This was first used with success by the investigators in the Bombay Plague Laboratory, where their work on the rat-flea infection theory could never have been carried out but for their protection by inoculation, as the workers could not *otherwise have avoided infection* while handling infected rats and their fleas. Haffkine's original vaccine has been greatly improved by Lamb and Liston, and more recently by Sokhey, so that it is now effective without causing severe and prolonged febrile and local reactions which resulted from the earlier vaccines. The value of inoculation can be gathered from the statistics published by Glen Liston, which show 7·96 cases per mille and a case death rate of 39·5 per cent. among 118,148 inoculated, against 34·4 cases per mille and a case mortality rate of 78·6 per cent. among 321,021 uninoculated in the same places at the same times. Bannerman found that the immunity lasts for from six to twelve months or more. *Among a large number of municipal employees, all of whom* were greatly exposed to plague infection, the incidence was 0·19 and the deaths 0·18 per mille in the inoculated, against 6·7 and 6·2 per mille respectively among the unprotected, a reduction to under one-thirtieth.

Living attenuated-plague vaccines have been extensively used in the Dutch East Indies and in Madagasgar, with material decrease in the incidence of the disease. L. Otten in Java found that three doses of dead vaccine protected only 30 per cent. of rats from death, but a single large dose of a living avirulent vaccine protected 87 per cent. of rats against inoculated plague. He therefore carried out a carefully controlled test in which nearly half the population of two districts were immunized *voluntarily by his living vaccine, with the result that the* plague death rate during two months of an epidemic was 1·01 in the inoculated against 4·75 per mille in the controls. G. G[illegible]rd with a

cases the primary bubo appears in the groin, in 15–20 per cent. in the axilla, and in about 10 per cent. in the submaxillary region ; in the latter case the disease may easily be mistaken for angina Ludovici.

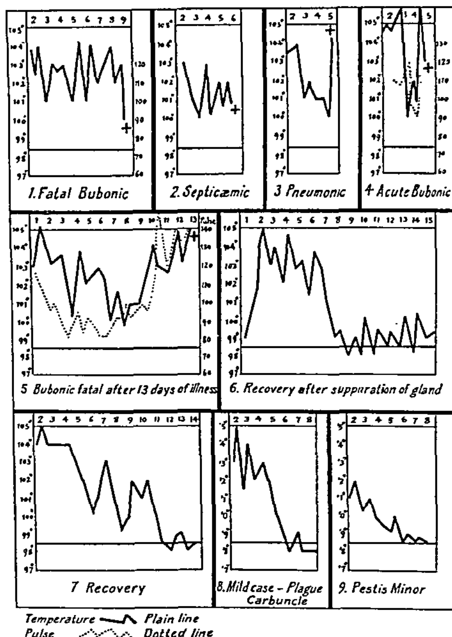


FIG. 40. Temperature chart of plague.

The more frequent occurrence of the bubo in the inguinal region is usually considered to be due to the fact that more flea-bites occur on the lower extremities owing to the rat-fleas living on the floors of rat-infested houses, but according to V. G. Heiser, accidental hypodermic inoculations of plague bacilli in the upper arm in the Philippines gave

is moderate general enlargement and congestion of the lymphatic glands without the formation of a typical bubo. The pneumonic lesions of plague are of the conglomerate broncho-pneumonic type, and somewhat resemble those seen in influenzal pneumonia.

The skin may show dark patches due to hæmorrhages ; it was probably because of these that the disease was called " black death " in the Middle Ages. Hæmorrhages are also common in all serous membranes. The spleen, liver, alimentary mucous membrane and kidneys show congestion and degenerative changes.

Clinical Description

The incubation period of plague is usually about three days, but is said to vary from two to ten days ; rarely it may extend to as long as fifteen days.

The general symptoms common to the bubonic, septicæmic and pneumonic types of plague are prodromal pains, malaise and mental apathy in some cases ; these are followed by the onset of chilliness and a sudden rise of temperature to about 103° F., with soft rapid pulse and respiration. There is severe frontal headache with pain in the back, and a characteristic feature of diagnostic importance is the rapidity with which congestion of the conjunctiva, restlessness, unsteady gait, slow speech, with great mental dulness and prostration develop. The patient is obviously very ill, although fever may have been present for only a day or two.

The temperature curve is of the high continued or remittent type ; there is sometimes a temporary deceptive remission shortly before death, but the pulse becomes increasingly rapid, even when the temperature is falling, in fatal cases. In the mild bubonic cases the temperature begins to fall by lysis about the fifth day, and takes two or three days to reach the normal. If suppuration of the bubo takes place, fever of an intermittent type goes on until the pus is evacuated, and in all but the mildest cases convalescence is prolonged (*see* Fig. 40, Charts 1 to 9).

Pestis minor is a rare, very mild type of bubonic plague without any severe constitutional symptoms. There is slight fever with enlargement of glands ; some of these cases may be ambulant and very difficult to diagnose, except by cultivating the *P. pestis* from fluid removed by gland puncture. Their occurrence in close relationship to other pronounced cases of plague ought to arouse suspicion.

The opposite mistake of suspecting cases of venereal disease and climatic bubo to be pestis minor is much more frequent, especially when plague is already prevalent not far away and the occurrence of the disease is expected. In all doubtful cases bacteriological confirmation is of the utmost importance.

Bubonic plague is by far the commonest type in ordinary outbreaks, and is easy to recognise. In from two-thirds to three-fourths of the

show very extensive consolidation. For this reason the physical signs may consist only in slight loss of resonance and the presence of coarse rales, and herpes is absent, according to Childe. Buboes are not noted, but slight swelling of the superficial lymphatic glands and enlargement of the spleen may be observed. The sputum is less viscid than in lobar pneumonia and is of a dark prune-juice colour. It contains enormous numbers of bi-polar staining plague bacilli ; these are of diagnostic importance, but may be mistaken for pneumococci. The patients rapidly become delirious and expectorate freely in all directions, and so they are highly infectious ; it is common for everyone living in one-roomed huts with such a case to contract the disease, which is almost invariably fatal, usually within two to four days. This variety is fortunately uncommon in India, except in the colder north-western regions and the Kashmir hills. The worst outbreaks have occurred in north-eastern Asia in the very cold winter season among overcrowded people, and in the higher parts of Madagascar plague pneumonia is met with where the temperature falls below 14° C., but is not seen when it is above 16° C. In Manchuria Wu Lien Teh has reported a latent form of plague affecting the lymph glands of the Siberian marmot by means of which the disease is carried over from one season to another.

Outbreaks of pneumonic plague in temperate or hot climates usually subside after a brief period of activity ; the infectivity of the droplet infection seems to diminish rapidly with successive transmissions and when the disease occurs in the absence of bubonic plague the infection seldom persists in the infected locality.

The blood changes in bubonic plague were found by the writer to consist in an increase in the number of red corpuscles, sometimes to 6,000,000 in the early stages ; this is accompanied by a moderate degree of leucocytosis during the first three days of the disease, not usually exceeding 20,000, but in the septicæmic form the leucocytes may rise to from 20,000 to 60,000, and counts of even 100,000 have been recorded. The differential leucocyte count in half the writer's cases showed a high proportion of lymphocytes during the first three days of the disease. This unusual form of lymphocytosis may be of diagnostic importance, as in the case of a European patient in Calcutta who was thought to be suffering from angina Ludovici, but the presence of a well-marked lymphocytosis in a blood smear led the writer to diagnose plague with a cervical bubo. The monocytes are few, and the presence of a high proportion of these corpuscles in one patient in a plague ward led to a successful search for malarial parasites and effective quinine treatment.

Plague bacilli can be detected by blood culture in nearly all severe cases of plague, whether of the septicæmic, bubonic or pneumonic type.

Mortality and Prognosis. Both primary septicæmic and pneumonic cases are almost invariably fatal, although Wu Lien Teh has reported rare recoveries from pneumonic plague. E. W. D. Greig reported a

rise to primary inguinal buboes in the majority of the cases. Clinically, the buboes are characterised by exquisite tenderness and a soft boggy feeling due to œdema of the tissues around the glands ; the individual glands are not palpable, although they are discrete. The thigh is flexed or the arm extended at right-angles to the body to relieve pressure on the painful glands. In the mildest cases the buboes may subside rapidly, but in more severe ones suppuration often occurs during the second week of the disease ; after incision the wound commonly takes several weeks to heal.

Carbuncles may rarely appear on the skin and may be surrounded by small vesicles containing a pure culture of plague bacilli, or there may also be streptococci. Such cases have been mistaken for anthrax, as occurred in a woman who had this kind of lesion over the breast, with the result that a surgeon proceeded to excise it. Pustules and carbuncles may sometimes be multiple and fatal, but the occurrence of primary vesicles is often an indication of low virulence of the infection, and recovery is likely to take place.

Septicæmic Plague. In this the same general symptoms occur, together with some general enlargement of the lymphatic glands, but there is no localised bubo. The disease is essentially a general plague septicæmia, there are numerous plague bacilli in the blood stream ; these may be seen in smears or they may be cultivated very readily. The disease runs a rapid course, and terminates fatally in 95 per cent. of bacteriologically verified cases. When septicæmic plague occurs in the absence of bubonic cases, it may be very difficult to recognise. In an outbreak in Colombo in 1914, no less than eighteen out of nineteen cases were septicæmic, all occurred within two weeks. The occurrence of a number of rapidly fatal cases of fever in an area near the docks aroused suspicion, and the nature of the disease was disclosed by post-mortem and bacteriological examinations. In ordinary outbreaks a small percentage of the most virulent cases are of the septicæmic type, but the simultaneous occurrence of bubonic cases makes them easy to recognise. The temperature may be comparatively low, due to overwhelming toxæmia, and death often takes place in one to three days ; but if the patient survives longer, a bubo may appear late in the disease, so that there is no sharp line of distinction between the septicæmic and the bubonic types.

Pneumonic plague is fortunately even more rare than septicæmic, except occasionally in cold climates such as that of Eastern Siberia and Manchuria. Early in the 1896 Bombay outbreak L. F. Childe met with a number of rapidly fatal pneumonia cases in the sputum of which he found a pure culture of the *P. pestis.* In these cases the physical signs in the lungs are slight in comparison with the severe constitutional disturbance ; this is due to the fact that the broncho-pneumonic patches are deep-seated, and only come to the surface of the lungs over small areas, but after death the central portions of the lungs may

form, preferably given intravenously in severe cases of plague. It has also been advised for prophylactic use in contacts of pneumonic plague cases.

In East Africa, D. Plum, as the result of the treatment of a large number of cases of plague at Nairobi hospitals, concluded that sulphapyridine acts almost as a specific in early bubonic cases, if given in large doses, such as 2 gm., for the first, followed by 1 gm. doses every two hours until the temperature remained normal for twenty-four hours.

In pneumonic cases the Bombay workers failed to save any of four cases treated by sulphathiazole, in spite of the blood remaining sterile. Possibly serum might have helped. On the other hand, L. van Hoof, in the Belgian Congo, obtained recoveries in 2 of 12 pneumonic cases treated with astreptine.

Streptomycin has furnished still more satisfactory results in plague cases, in 3 gm. doses every four hours until the temperature becomes normal, usually in two or three days. Sulphonamides may be used with it. In Bombay in septicæmic cases, with from 1 to 300 colonies of plague bacilli per 0·25 c.c. of blood, the mortality was nil against 4–19 per cent. in 45 cases treated with sulphadiazine ; it was 27 per cent. against 50 per cent. in 3 and 8 cases respectively with over 390 colonies in the same amount of blood. Thus the results of treatment of plague have been greatly improved.

Aureomycin and chloromycetin have been found by Sohkey very effective in the treatment of experimental plague in mice. These new drugs appear to be worthy of trial in human cases.

General Treatment. The fever should be treated on ordinary lines ; good nursing is the main essential, and cold should be relied on to control the temperature when necessary, but depressing antipyretics are contraindicated in this exhausting disease. Morphia is often necessary to lessen the pain and induce sleep ; belladonna and glycerine applications to the buboes may be of use in mild cases ; early incision should be resorted to if suppuration occurs. Iodine and ichthyol dressings have been advised after incision. Cardiac tonics are often used ; the diet should consist of liquids, mainly milk. The injection of iodine, both into the buboes and intravenously, has been recommended, but its value is doubtful.

II. TULARÆMIA

Definition. A plague-like infection of small wild rodents such as rabbits, hares, field mice, rats, lemmings, squirrels and hamsters. It is transmitted to man by the bites of various arthropods, by contamination of water supplies, by direct contact with infected carcases or by errors in laboratory technique.

Distribution. Originally described in Tularense County in California in 1911 as a plague-like disease of rats, it has been found in Norway,

mortality of 97 per cent. in cases from which he cultivated the *B. pestis* from the blood during the first three days of the disease, but in bacteriologically negative cases the death rate was only 43 per cent. Thus in secondary as well as primary septicæmic cases the prognosis is about as grave as it can well be. In a series of 444 hospital plague cases in Bombay, the Indian Plague Commission recorded a mortality of 30 per cent., but no patient with over 10 plague bacilli per ¼ c.c. of blood recovered.

Clinically, in the early stages, the symptoms give *little* clue to *the* prognosis. At a later stage high prolonged fever with delirium and very rapid pulse of low tension are unfavourable signs. If the patient survives until the bubo suppurates he generally recovers ; good nursing increases his chances.

Diagnosis. In the pneumonic and septicæmic types the diagnosis can only be made with certainty by finding the *B. pestis* in the sputum and blood respectively, although, if cases of either occur while typical bubonic plague is prevalent, there may be little doubt as to their nature. The death of rats from plague in the same or in a neighbouring house is strong evidence in favour of plague. During the prevalence of plague the characteristic bubonic cases with severe constitutional symptoms will be easily recognised ; here again the finding of dead rats will often be the first occurrence to arouse suspicion. Discovery of the plague bacillus by puncture of the glands will furnish conclusive evidence in these and also in the rare pestis-minor variety which is more liable to be overlooked. Post-mortem it has been found that in infected animals in hot climates pure cultures can be obtained from the bone marrow up to three or four days after death. A finger bone sent to a laboratory will suffice for the purpose. The bacillus has been cultivated in a virulent state from the femur marrow of dead rats and guinea-pigs up to eight to ten months. In the Belgian Congo the inoculation of young animals with the bone marrow of numerous rats enabled the distribution of plague to be mapped out.

Treatment

Anti-plague serum has been in use for many years with variable results. Earlier trials in Bombay showed little benefit in bacteriologically confirmed cases, but *later the use of a more potent* serum, made by F. P. Mackie and Naidu by the injection of highly virulent plague bacilli into calves, furnished better results on intravenous injection. It is more costly and keeps less well than the sulphonamide drugs.

Sulphonamides were found to have bactericidal action in plague-infected guinea-pigs. A trial in Bombay in dangerous *septicæmic* cases in man gave case mortalities of about 40 per cent., against 95 per cent. after the use of the former iodine treatment and of 60 per cent. under the serum treatment. Sulphadiazine appears to be the best

jecting morphine with dirty syringes. The disease is now known to exist in Burma, Malaya and Ceylon.

Ætiology. *Bacterium whitmori* is a small bacillus closely resembling *B. mallei*. It is pathogenic to most laboratory animals and in guinea-pigs produces acute orchitis (the Strauss reaction).

Pathology. Caseating nodules form in the internal viscera ; these break down to form honey-comb suppurating areas. *B. whitmori* is readily cultivated from these abscesses and from the blood.

Symptoms. The disease is rarely diagnosed during life. In some cases vomiting and purging with acute dehydration may occur. In others prolonged irregular pyrexia is found ; there may be multiple localised subcutaneous abscesses with prolonged suppuration. Stanton and Fletcher have described pneumonic, bubonic, typhoid and renal types.

Diagnosis. This depends on cultivation of the specific organism from the blood, sputum, urine or pus. The serum readily agglutinates cultures of the organism in high titres.

Treatment. *B. whitmori* is sensitive to chloramphenicol *in vitro* ; heavy doses of that antibiotic may be tried if a diagnosis is made during life.

LEONARD ROGERS

Asia Minor, Siberia and Japan. As its distribution is possibly world wide, specific tests for its recognition should be carried out in the investigation of any fever which cannot be diagnosed by other means.

Ætiology. The disease is caused by a minute gram negative cocco-bacillus *Brucella tularense*, 0·3μ by 0·2μ in size. It stains with difficulty. It grows on serum-glucose-agar if a portion of guinea-pig spleen is added. Inoculation of infective material into a rat or guinea pig produces septicæmia with intense infection of the spleen.

Transmission. Gad flies (*Chrysops discalis*), horse flies, bugs, mosquitoes, ticks and rabbit lice have all been incriminated. Water supplies in Norway have been found to be infected by dead lemmings.

Pathology. In some human cases there is local ulceration at the site of the bite with lymphadenitis in the glands of the drainage area. No characteristic pathological changes have been found in human cases contracted in laboratories, even the mode of entry to the human body in such cases being unknown.

Symptoms. The disease may occur as a generalised febrile infection without localising symptoms. The onset is sudden, with headache and severe pains all over the body. The pyrexia may last from three weeks to a year or more in untreated cases. After the fever declines irregular recurrences are common and a severe degree of lassitude and debility is usual. In trappers and rabbit dealers a local papule followed by an indolent ulcer with lymphadenitis is commonly found in addition to the irregular fever. An ocular variety with conjunctivitis, chemosis and glandular swelling has been described.

Diagnosis. The diagnosis depends on specific agglutination reactions which develop about the fourteenth day of the disease. The inoculation of blood or of glandular material obtained by biopsy into a guinea pig enables the organism to be cultivated from the spleen.

Prognosis. Before the introduction of antibiotic therapy the outlook was much the same as that of Undulant Fever. Prompt treatment now terminates the infection.

Treatment. Streptomycin given intramuscularly in 2 gm. doses daily for two days followed by 1 gm. doses for five days terminates the infection. Aureomycin given by mouth in doses of 2 gm. daily for a week gives equally good results. General measures to deal with the inevitable post-febrile debility are necessary.

Prophylaxis. Masks and gloves should be worn in handling infective material.

III. MELIOIDOSIS

Definition. A glanders-like disease occurring in rodents. It is occasionally found in man but the mode of infection is unknown.

Distribution. The disease was originally described in man by Whitmore in Rangoon where he found the characteristic lesions in the post-mortem examination of beggars who had been addicted to in-

dusty, dry summer months. Cases used to be particularly frequent in the military hospitals until the use of unboiled milk was prohibited, and the disease practically disappeared as a consequence of that order. Outbreaks due to goat's milk have appeared in ships, and the disease has been carried to fresh places by the importation of infected goats from the Mediterranean area. Young children and old people are said to be less susceptible. The disease appears to have been imported into South Africa and India by British troops previously infected in Mediterranean stations and it is noteworthy that in India the disease has been almost confined to the Punjab, where the largest numbers of British troops are stationed, and infected goats were found there by W. C. H. Forster.

Ætiology. The causative *Br. melitensis* is a very minute organism which was cultivated by D. Bruce from the blood and spleens of fatal cases; it can also be obtained from the blood during high fever, as well as from the urine. After the first week or two of the disease the blood of the patient agglutinates the organism.

Infection also takes place readily in laboratories among those who handle cultures of the causative organism, and it appears to be likely that direct infection results not infrequently from handling infected carcases, milking infected animals, or working in fields contaminated by their urine.

In 1912 Nègre and Raynaud, in Algeria, found a *Br. paramelitensis* in cases of the closely related paraundulant fever; the blood of the patient agglutinated this organism in high dilutions, but not the ordinary *Br. melitensis*; and others have since reported similar cases. Monkeys can be readily infected by feeding them with cultures or infected goats' milk.

The *Bacillus abortus* of Bang, produces contagious abortion in cattle, horses, goats, pigs and can also infect man; it is also agglutinated by the blood of undulant-fever patients, and in South Africa and elsewhere this organism has been proved to produce fever in man closely resembling undulant fever. Serological investigations by Alice C. Evans and others have shown that these closely allied bacteria can only be differentiated from each other by elaborate agglutination and absorption tests requiring laboratory experience, so it has been suggested that they should be classed together in a group called *Brucella*. *Br. abortus* infections may, however, be very common in cattle with few infections in man, as in Melbourne, with 24·5 per cent. of farm milks found to be infective when fed to guinea-pigs, although no human undulant fever cases had been met with there. This may be explained by the observation of Theobald Smith that bovine strains in the United States had low pathogenicity, but porcine and caprine ones were much more virulent. In the same country it has been observed that human abortus infections are much less commonly due to drinking infected milk than to handling freshly-cut

CHAPTER X

BRUCELLOSIS
(UNDULANT FEVER AND ABORTUS FEVER)

Undulant Fever (Malta fever) is a specific disease caused by the *Brucella* (*Micrococcus*) *melitensis*, which is usually conveyed by drinking the milk of infected goats. The disease runs a very prolonged course with waves of remittent and intermittent fever; there also occur enlargement of the spleen, effusion into joints and orchitis.

Abortus fever, discovered by Bang in 1897, is very similar, and is due to *Brucella abortus*, usually derived from infected animals or their corpses. Undulant fever and abortus fever can be regarded as different forms of brucellosis.

Historical. In 1859 Marston first differentiated the disease clinically from typhoid fever and named it "Maltese fever."

In 1881 Veale described the disease and differentiated it from malaria.

In 1886 Sir David Bruce demonstrated its specific nature by isolating the *Micrococcus melitensis* from cases and reproducing the disease in monkeys. These three investigators were all British Army medical officers.

In 1897 Sir Almroth Wright established the diagnostic value of the agglutination reaction, which enabled the disease to be recognised in India, China and other places remote from the borders of the Mediterranean.

In 1906 Sir David Bruce's Commission, working in Malta, found that the common mode of infection was through drinking goat's milk. This discovery has enabled the disease to be nearly stamped out of the British Navy, with a remarkable reduction in the sickness and invaliding rates.

Geographical Distribution. Undulant fever occurs in the countries around the Mediterranean Sea, Egypt, the Sudan, East Africa, South Africa, North-West India and the Far East, etc. This wide incidence led Hughes, in his monograph on the disease of 1897, to suggest the descriptive name of undulant fever, in place of the misleading geographical term "Malta fever." The disease has spread rather extensively in Southern France since 1900. In 1926 no less than fifteen departments were found to be infected, and at least 3,000 cases occurred between 1920 and 1926.

Abortus fever is widely distributed in Europe, the United States, South Africa, the Dutch East Indies and other countries.

Epidemiology. The seasonal incidence of undulant fever has been chiefly studied in Malta, where the disease is most prevalent in the hot,

CLINICAL DESCRIPTION

The incubation period is about one to two weeks ; it may be as short as five days after accidental inoculation.

The onset is rather insidious, like that of typhoid. The duration of the disease is so extremely variable that it was said by Bassett-Smith to vary between three weeks and two years.

In fulminant cases the temperature is of the high continued type, the disease may commence suddenly and prove fatal in five to twenty days. These cases closely resemble typhoid, for which they may be mistaken. At the other extreme are **mild cases** with only intermittent fever of a few weeks' duration and rather indefinite symptoms—these are difficult or impossible to recognise without the aid of laboratory tests.

The undulant type is by far the most frequent one ; it presents a series of waves of high remittent fever, each lasting from a few days to several weeks, but usually about two weeks ; these are separated from each other by periods of normal temperature or slight intermittent fever of from three to ten days' duration, during which the general symptoms are also in abeyance. At any time in the long course of the disease severe relapses may occur, and even terminate in fatal hyperpyrexia.

The constitutional symptoms accompanying the fever include lassitude, increasing anæmia, especially in prolonged cases, and profuse sweats, with the daily remissions of temperature. The pulse is variable and irregular and the heart may be irritable. The blood pressure is usually low ; phlebitis may occur. There is restlessness, and pain, especially over the spleen and liver or in the joints ; hyperæsthesia of the feet, and neuralgic pains, referred usually to the intercostal and sciatic nerves are common. The hair may fall out, but it grows again after recovery.

The blood shows a moderate degree of anæmia with red counts which seldom fall below 2,500,000 ; the white cells are decreased in proportion to the red, with a relative decrease in the polymorphonuclears and a corresponding relative increase in the lymphocytes.

The Digestive System. The tongue is persistently white, furred and flabby, there is troublesome constipation as a rule, and the breath is offensive. Flatulence and abdominal discomfort, associated usually with a poor appetite, occur during the height of the fever, but subside during the remissions ; at this time the diet should be increased cautiously because over-feeding is suspected by some to increase the danger of relapse.

The spleen is enlarged from an early stage and often to a considerable size ; it may even reach the level of the navel ; the organ is soft, so there is danger in making a puncture for diagnostic purposes. There is often tenderness of the spleen. The liver is also enlarged and tender due to congestion of the organ.

tissues of cattle and pigs; Hardy and others found that 73–81 per cent. of guinea-pigs could be infected through the unabraded skin after shaving or clipping the hair, so this mode of abortus infection appears to be the most likely one in man.

B. melitensis is excreted in the urine of patients, and it is not killed by drying or by cold, so that it may possibly be blown about in dust and cause infection through the air passages. It can live for a number of days in water or milk, even when the latter has become acid; it can also survive in butter and fresh cheese, which are other sources of infection.

Prophylaxis. This is based on the ætiological data just considered, so it may most conveniently be dealt with next. The importance of prohibiting the use of goats' milk in the endemic areas is proved by the data of P. Bassett-Smith, who showed that there were 780 cases of undulant fever in the British Navy in 1904, and only twelve in 1907 after the prohibition of the use of unboiled milk, while during World War I with a much increased personnel, the cases averaged only 12·8 yearly. This practical elimination of a serious disease is a remarkable example of the immense value of medical research. Unfortunately, among the indigenous population of Malta, comparatively little reduction of the disease was brought about, as the people have refused to adopt the simple measures which were recommended. Further, in the civil population, there are many other sources of infection besides the drinking of goats' milk, and it is difficult to eliminate the handling of infected animals and infected soil. The urine and fæces of patients should be sterilised.

Earlier attempts to immunize goats against *Br. melitensis* infections failed, but Zammit reported promising results with Besredka's intradermal injections of broth cultures. Ascoli and Sanfelippo have immunized goats by two massive inoculations of killed cultures, and C. Cerruti has reduced the abortion rate in goats from 32 to 1·3 per cent. by injections of formolised broth cultures.

Since the slaughter of goats whose blood or milk agglutinated the *Br. melitensis* has been enforced in Malta, infected animals have been reduced to under one-half of their former numbers, and the incidence of undulant fever had also fallen to about half, according to Eyre. Butter and fresh cheese, as well as unboiled milk must be avoided. In countries such as Rhodesia, where undulant fever has occurred in relation to epidemic abortion in cattle in the absence of goats, infection from such cattle must also be avoided. Only dead cultures should be used for agglutination tests, owing to the danger of laboratory infections by live cultures.

Nicolle and Conseil report successful immunization of man on a small scale, both by subcutaneous injections of dead *Br. melitensis*, and by their oral administration in large doses on three consecutive days; they controlled their tests by injecting live cultures.

serious affection to be recognised and effectively treated. Tuberculosis may be more difficult to differentiate, but the continued absence of a positive agglutination of the *Br. melitensis* should cause the former disease to be suspected.

Acute rheumatism is rather uncommon in the warm countries where undulant fever prevails, so in the endemic areas fever with ephemeral swelling and pain in the joints should always arouse a suspicion of undulant fever and lead to the performance of an agglutination test. In endocarditis and other septic infections leucocytosis will be present.

The temperature charts of the more insidious and chronic types of amœbic hepatitis may be similar to those of undulant fever, there are copious sweats in both affections, but the characteristic leucocytosis of amœbic hepatitis is sufficient to exclude uncomplicated undulant fever.

Agglutination Test. Reactions in dilutions of 1 in 40 to 1 in 100 are obtainable in most, but not in all cases, of two or more weeks' duration. They should be carried out by the macroscopical method, using suitable dead cultures.

Cultivation of *Br. melitensis*. When a laboratory is available the most certain method of diagnosis is the cultivation of the *Br. melitensis* from the blood of undulant-fever patients. Spleen puncture to find the organism is not justifiable on account of the danger of intraperitoneal hæmorrhage owing to the softness of the organ. Amoss and Poston have frequently obtained cultures from the suspensions of stools after having removed the centrifuged sediment and treated the supernatant fluid with immune serum to clump any organisms present, and the flocculi thus formed are planted out on Teague's medium. *Br. melitensis* may occasionally be cultivated from the urine.

An intradermal inoculation test has been introduced by E. Burnet and confirmed by others, who have reported it as more reliable even than the agglutination test after the first seven to ten days of the fever. A twenty-day broth culture of the *Br. melitensis* is passed through a porcelain filter, boiled for one minute and then preserved with 0·5 per cent. carbolic acid, when it will keep in a cool place for several weeks in sealed ampoules. One-tenth of a c.c. is injected intradermally on the inner side of the upper arm ; a positive reaction consists in the appearance in six hours of a ¼-inch patch of redness and œdema with slight pain, which persists for about forty hours. Giordana reports better results by using heat-killed salt suspensions of recently isolated strains in place of broth cultures.

Prognosis. The mortality is only 2 per cent. in military hospitals, according to Hughes, but it may be as high as 9 per cent. in an unselected civil population. The majority of the deaths occur in the first three weeks in malignant attacks ; after that period the chances of ultimate recovery are very good, although Bassett-Smith warned against too sanguine a prognosis, as at any time a severe and fatal recrudescence

The nervous system is severely affected in this prolonged debilitating fever, there are pains in the head, back and limbs early in the disease; severe neuralgia, which may affect almost any nerve, is common in the later stages of the disease. Other nerve symptoms are aphasia, hyperæsthesia, actual neuritis or sciatica, sometimes accompanied by temporary muscular paralysis and atrophy and troublesome sleeplessness. These manifestations appear to be of toxic origin.

The complications of undulant fever are also numerous, they include bronchitis or broncho-pneumonia during the acute fever, and myocarditis or rarely actual endocarditis, which Bassett-Smith met with in two out of 750 cases. Orchitis of short duration occurs in 6 per cent. of cases, while in women there may be mastitis with the *presence of the Br. melitensis in the milk, which may then be infective* to children at the breast. Abortion or premature delivery may occur during high fever. Bevan has recorded long-continued blood-stained involuntary seminal emissions in man such as occur in bulls infected with *Br. abortus.*

Joint involvement is of frequent occurrence in this disease. At some time or other in a large proportion of cases one or more joints become swollen and painful for a day or so, and then the trouble shifts to another until most of the joints have been affected. The condition may closely resemble acute rheumatism, but according to Bassett-Smith the most painful joints are the sacro-iliac; actual effusion into the joints seldom occurs, and salicylates are useless in treatment. Bone abscess has been recorded.

The Urine rarely shows more than a trace of albumen. Hæmaturia has been recorded.

Italian authorities report that undulant fever is not uncommon in children, in whom it runs a long course with a mortality of 6 per cent.

Diagnosis. The difficulties in the recognition of undulant fever in its early stages are such that Bassett-Smith pointed out that nearly every case had been treated for malaria or some pyogenic affection before a correct diagnosis was made. Practitioners should, therefore, always be on the look out for it in areas where it is known to prevail. Malaria should first be excluded by an examination of blood films; these will also show the absence of leucocytosis and so serve to exclude a number of fevers in which that blood change occurs.

Among the fevers of long duration which are most likely to be confused with undulant fever are kala-azar and obscure tuberculosis. Fortunately, undulant fever is unknown as an indigenous disease in the great home of kala-azar in North-Eastern India, but in the Mediterranean area both diseases occur, and the temperature charts may be very similar. The disproportionately great reduction of the white corpuscles as compared with the red is found only in kala-azar, and finding the parasites of the latter disease by spleen or liver puncture (p. 75), or more simply a positive aldehyde test (p. 75), will enable that

CHAPTER XI

AMŒBIC DYSENTERY

Definition. Amœbic dysentery is the form of dysentery which is caused by *Entamœba histolytica*. The parasite acts chiefly on the submucous coat of the large intestine and produces ulceration varying from a very acute to a very chronic type ; this is liable to be followed by amœbic hepatitis and liver abscess. The symptoms are those of dysentery or chronic diarrhœa ; the disease may be difficult to eradicate completely.

Historical. In 1875 Losch, in Russia, reported finding entamœbæ in dysenteric stools.

In 1883 Koch recognised the entamœbæ in the stools of cholera patients in Egypt, and Kartulis soon after found them in numerous cases of dysentery in the same country, but owing to the fact that the stools of some 50 per cent. of the healthy persons also contained entamœbæ they were not then accepted as the cause of Egyptian dysentery ; many of them doubtless were *E. coli.*

In 1887 Kartulis found entamœbæ in the pus of a liver abscess.

In 1890 Osler found the organism in a dysentery case in Baltimore, and his pupils, Councilman and Lafleur, in the following year described the characteristic lesions in the bowel, and called the disease amœbic dysentery ; curiously enough they considered ipecacuanha useless in its treatment.

In 1902 L. Rogers showed that amœbic dysentery is very common in India, where it had not previously been differentiated and described, and he soon recognised the fact that ipecacuanha is a specific for amœbic dysentery and for amœbic hepatitis, but useless in bacillary dysentery. He also showed that amœbic hepatitis and liver abscess were always secondary to amœbic ulceration of the large bowel, often of a latent nature and limited to the cæcum and that the pus of liver abscess was nearly always sterile as regards bacteria.

In 1908 Schaudinn differentiated the *E. histolytica* from the harmless *E. coli* with which it had formerly been confused, and in 1913 Walker and Sellards, in the Philippines, demonstrated by experiments on prisoners that *E. histolytica* is pathogenic to man, but *E. coli* is harmless.

In 1906 L. Rogers reported the successful treatment of amœbic liver abscess cases by aspiration and oral administration of ipecacuanha. In 1907 he demonstrated that liver abscess could be prevented from developing by the recognition of the pre-suppurative stage of amœbic hepatitis by the occurrence of leucocytosis and treating it by large doses of ipecacuanha (*see* p. 242).

In 1912 L. Rogers demonstrated the specific action in amœbic disease of injections of emetine, the active principle of ipecacuanha.

of the fever may occur. Moreover, it is quite unsafe to give any prognosis regarding the probable duration of the fever until the temperature, pulse and tongue have been normal for ten days, when it is safe to assume that the disease is at an end ; even then there is a prospect of several weeks of convalescence before complete recovery after a prolonged attack. The recently discovered antibiotics, chloromycetin and aureomycin are of value ; the last may produce a cure in a week or two.

TREATMENT

With the exception of the antibiotics just mentioned there is no good evidence that any drug has a definite specific effect in undulant fever. Nursing and the treatment of any distressing symptoms as they arise, and maintaining the strength of the patient with easily assimilable food are important. If the temperature rises to over 103° F. tepid sponging is required, and a rise to 104° F. should be regarded as a danger point, necessitating cold sponging or the wet pack. Care must be taken not to check the copious sweats, which reduce the temperature ; depressing antipyretics, such as phenacetin, should be avoided in this chronic debilitating disease. Constipation requires attention, and trional or sulphonal are recommended for sleeplessness. Small doses of iron and arsenic with tonics may be required in the later stages to combat anæmia and weakness. Bassett-Smith recommended yeast in 2-drachm doses twice daily in milk or with bread and butter ; he thought it useful in increasing the leucocytes and supplying vitamin B. Belladonna liniment or opium fomentations may be required for the relief of pain in the affected joints.

Abortus fever differs from undulant fever in being caused by *Br. abortus* transmitted to man from bovine animals or by *Br. suis*, transmitted from pigs. The disease is less severe than undulant fever, especially the disease caused by *Br. abortus*, but it may be very chronic. Treatment is on the same lines as for undulant fever.

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potassium iodide, 2 per cent., which stains the nuclei yellow; the examination is made with a high-power dry lens. The fully developed cysts of *E. histolytica* and *E. coli* usually measure 5 μ to 20 μ and 10 μ to 30 μ respectively; the former shows four ring-shaped nuclei and the latter eight, which enables them to be easily distinguished, although a few developmental forms with a smaller number of nuclei may be met with. Cysts of the other two common varieties of non-pathogenic entamœbæ are smaller on the average and measure up to 10 μ to 12 μ. Those of *Endolimax nana* are oval in shape, and those of *Iodamœba butschlii* are irregular and contain large inclusions staining a mahogany colour with iodine.

For bringing out the finer structure of entamœbæ in mucus spread on cover-glasses, wet films should be fixed and stained with iron-hæmatoxylin and differentiated with a mordant to remove over-staining; this requires experience. Clifford Dobell has described simpler methods in which the films are left in either 2 per cent. solution of phosphotungstic acid, or in ammonium molybdate for ten minutes or more, washed in several changes of distilled water and ripened in 0·2 per cent. aqueous solution of hæmatoxylin for fifteen to twenty minutes or longer and then kept in tap water till they become purple before mounting; overstaining is thus avoided.

Owing to the large size of the vegetative forms, with a little practice they can often be detected with a low-power of about 50 diameters; the high-power lens can be turned on to verify the observation. It is necessary to insist that special instruction in the microscopical diagnosis of amœbic dysentery is essential; many cases of bacillary dysentery have been recorded as being amœbic because macrophage and epithelial cells have been mistaken for entamœbæ. As Faust has pointed out, the presence of *E. coli* indicates the likelihood of *E. histolytica* infection, for the incidence of the two forms increases and decreases together.

Distribution and Pathogenicity of *E. histolytica*. The pathogenic human entamœba in its active vegetative stage has great powers of penetrating human tissues, and it readily passes through the mucous coat of the large bowel into the submucous layer, where it multiplies greatly, and gives rise to a gelatinous exudation containing comparatively few cells and causing great thickening of this part of the bowel wall so that it may even exceed the combined thickness of all the other layers. In acute cases the organisms may penetrate the muscular and peritoneal coats. The small radicles of the portal system in the vascular submucous layer are also penetrated, and the parasites thus pass to the liver, where they produce hepatitis and abscess formation as described under the liver complications. They may also pass from the liver through the general circulation to produce an abscess of the brain, and amœbic abscesses may also occur in the spleen and lungs. Many entamœbæ escape from the ulcers into the lumen of the

Ætiology. The *Entamœba histolytica* has now been firmly established as the cause of amœbiasis in general, and it is essential to be able to distinguish it from other varieties of human entamœbæ because, clinically, the different forms of dysentery resemble each other too closely to be clearly recognised without the aid of the microscope. In patients coming for treatment for active dysentery or diarrhœa the easily recognisable active motile stage of the protozoa will usually be found readily in the mucus present in the stool, but in the quiescent stage only the encysted forms may be present. It is also important to obtain as fresh a stool as possible; within two or three hours after being passed the causative parasite may have lost its typical movements and appearance. A full description of the minute structure as seen in stained specimens of the less common *Endolimax nana* of Wenyon and O'Connor, the *Iodamœba butschlii* of Dobell, and the rare *Dientamœba fragilis* of Jepps and Dobell, is beyond the scope of this work. They are all considerably smaller than the great majority of *E. histolytica* and *E. coli*, and so are liable to be confused only with the uncommon small strains of the former, and they do not resemble the pathogenic organisms in their movements. By repeated examinations in thirty-eight asylum inmates, sixteen infections with numerous *Dientamœba fragilis* were found by E. G. Hakansson in Panama. They yielded to 0·5 gm. of carbarsone twice daily for two days. Another observer reported that such human infections yielded in four days to emetine and treparsol. Of much more practical importance is the distinction between *E. histolytica* and the harmless *E. coli*, as their size is very similar; in the active vegetative stage they measure from 18 μ to 40 μ in diameter and usually only vary between 20 μ and 30 μ, against 6 μ to 12 μ of *Endolimax nana* and 9 μ to 13 μ of *Iodamœba butschlii* (*see* Colour Plate, Figs. 69–78).

The vegetative motile stage of *E. histolytica* is characterised by a fine granular ground-glass-like appearance of the endoplasm surrounded by clear ectoplasm, and its movement is a flowing one across the field of the microscope with an anterior extrusion of a clear pseudopodium. Vacuoles are absent in fresh specimens, a number of red blood corpuscles are usually included in the protoplasm, and the nucleus is an inconspicuous ring. *E. coli* has a less clearly defined ectoplasm, its movement is sluggish with protrusion and retraction of blunt pseudopodia; it does not actually progress across the field of the microscope. It has vacuoles and numerous inclusions of bacteria and granules, but not of red cells, the ring-shaped nucleus is rather more conspicuous, and the colour is often greenish. The differences in the movements and the presence or absence of included red corpuscles are the most important points of distinction in the living vegetative stage.

When looking for the encysted stage a fresh smear should be stained by the addition of a watery solution of iodine, 1 per cent., and

therapeutic experiments to discover remedies for human amœbiasis. In Moscow A. Awakjan in five of 400 rats examined found entamœbæ with the typical four-nuclear cysts of *E. histolytica* which proved pathogenic to cats on injection per rectum.

Cyst carriers are persons who appear to be healthy, but are found to pass *E. histolytica* cysts, which may be a source of infection to others. They are usually persons who have previously suffered from amœbic dysentery or diarrhœa and have not been completely cured, but in the endemic areas a certain number of persons who give no history of intestinal trouble may yet be cyst carriers. During the 1914–18 War they were found to be so numerous in the East that it was impracticable to isolate and cure them of the infection, and even among stay-at-home healthy inhabitants of England a small percentage of carriers have been found. In the United States Craig estimates the carriers at 5–10 per cent. of the population, and he argues that they all have slight bowel lesions and nearly all of them have lived in or visited endemic areas of the disease, so there are no really healthy carriers. Faust reports infections in up to 20 per cent. of the population in the U.S.A.

Cooks have been proved to be carriers of *E. histolytica* infection in China and elsewhere, so they should be investigated in any unexplained outbreak of the disease.

Flies may also be carriers of the *E. histolytica* cysts, which may pass unchanged through the insects which have fed on human excrement, and thus be conveyed to food.

Seasonal Incidence. Amœbic dysentery is usually evenly distributed throughout the year in tropical countries. In the U.S.A. the disease is most prevalent in the summer months.

Pathological Anatomy. Although the most essential lesion of amœbic dysentery is an inflammatory exudation into the submucous coat leading to necrosis of the mucous membrane with consequent ulceration, the severity and extent of the pathological processes vary so widely that very different anatomical and clinical conditions result. Thus, in the most acute sloughing type the resulting ulcers may involve the whole circumference of the bowel for inches, with enormous thickening of its coats, and every gradation is met with between these rapidly fatal gangrenous cases and those in which a few small chronic ulcers occur in the cæcum, giving rise to no definite symptoms. It will, therefore, simplify the description to begin with the early lesions and trace how they may progress into the most severe ones.

The first lesions appear as red dots or small patches of congestion of the mucous membrane with slight thickening of the submucous coat; neighbouring parts will show small round raised yellow areas surrounded by a rosy ring of acute congestion; the patches are raised well above the level of the surrounding healthy mucous membrane. This appearance is due to localised tawny-yellow gelatinous infiltration

bowel and are passed in the stools, mainly in mucus. As the looseness of the bowels ceases, the conditions become less favourable for the vegetative stage, and many of them encyst to form the smaller double-contoured resistant cysts, which may continue to be passed for a very long time ; these constitute the fotm in which infection is conveyed to other persons. The vegetative stage dies rapidly outside the body under ordinary conditions, but the cysts niay survive for several weeks under moist and cool conditions, and they may eventually gain access to a new host through food or water, and reproduce the disease. They survive for some hours in sewage, but not after filtration through 2 metres of soil, and are not killed by chlorination of water. Urine has a lethal action on the cysts, killing them in two or more hours. Hegner reported that high incidence of amœbic dysentery over a decade ceased during the year following the provision of a supply of pure drinking water. In 1933 in two Chicago hotels a number of acute amœbic infections were traced to a polluted water supply. In 1937 A. V. Hardy reported 3,100 out of 7,500 infections through drinking water infected after a fire. In Ceylon the treatment or transfer of eleven cooks and other food handlers resulted in the abrupt decline of new infections.

It was only in 1925 that *E. histolytica* was successfully cultivated by W. C. Boeck and J. Drbohlav on coagulated egg covered with one part of human serum to eight of Locke's solution ; subsequently the method was simplified by using Locke's solution, containing one part in seven of inactivated human or rabbit blood serum. Cysts are difficult to cultivate from stools, but with the addition of streptomycin to the culture medium positive results have been reported in 73 per cent. of attempts against 8 per cent. without this addition. Prolonged cultivation diminishes pathogenicity, unless the organism is caused to encyst periodically at a temperature of 4° C. Cultivation in increasing strengths of emetine solution is said to produce resistant organisms. Simple enteritis, induced by certain bacilli or by croton oil, may enhance the powers of *E. histolytica* to produce dysentery in animals. Cultures have been used for testing the effect of drugs on the organisms.

Animal infections may be readily produced in cats and dogs by the injection into the rectum or lower ileum of fresh material containing *E. histolytica* ; typical dysenteric ulceration of the large bowel results and this may be complicated by amœbic liver abscesses. Faust states that in the dog no entamœba cysts are formed so the dog cannot infect man, but Swartzwelder showed that the oral administration of un-encysted *E. histolytica* can infect dogs. Boyd has recorded an outbreak of amœbic dysentery in a pack of hounds in India traced to an infection of the boy attendant who fed them. Dobell and also Hegner and Stabler have described experimental infection of monkeys, and the former suggests that infected Macacas apes could be used for

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of the submucous coat, over the centre of which the epithelial layers of the mucous membrane have sloughed off, while the surrounding mucosa remains as an inflamed ring round the exposed exudation. Another stage will be evident in other parts of the bowel in the form of elongation of the raised ulcers along the transverse folds of the mucous membrane ; between these the mucosa remains quite healthy. Thus the early ulcers stand up as button-like raised patches from the healthy bowel wall, and so present exactly the opposite condition to the lesions of bacillary dysentery, in which depressed serpiginous ulcers occur on a generally thickened and inflamed mucous membrane, and it is surprising that the two diseases were not differentiated much earlier than they were. In this comparatively early stage the lesions are nearly always more numerous and advanced in the upper than in the lower portion of the large gut, and a light scraping from the floor of an ulcer will reveal numerous active *E. histolytica* if the post-mortem examination is made on a fresh subject.

Acute sloughing amœbic dysentery results from further development of the lesions just described, probably aided by secondary infection with bacteria from the bowel contents. The exudate caused by the amœbæ increases and the normally thin layer of the submucous coat thickens until it may reach several times the total normal thickness of the whole bowel wall, so that the gut may be felt through the abdominal wall as sausage-shaped or intussusception-like masses. In such cases the exudate will be found extending through the muscular coat to reach the subperitoneal layer, and the external surface will be covered by an exudate of lymph containing active amœbæ without any perforation being visible. The ulcers by this time extend over many square inches of the interior of the bowel, and black sloughing tags of gangrenous mucous membrane may be seen hanging from their edges. The wall of the bowel will be so softened in places that it closely resembles damp blotting paper, and it may be difficult to remove the gut post-mortem without tearing it to pieces. Fortunately, these extreme cases are not very frequent even in the tropics ; they occur almost entirely in debilitated persons. Innumerable minute abscesses may also be found in the liver. The ulcers are now generally distributed throughout nearly the whole length of the large bowel, but it is remarkable how they are almost invariably strictly limited by the ileo-cæcal valve, the under surface of which may be sloughing while the upper is free from ulceration. Even in the worst cases it is remarkable how considerable areas of the mucous membrane remain quite healthy close to huge sloughing ulcers.

Chronic amœbic dysentery produces still other appearances, owing to the original submucous exudation escaping or being largely absorbed, leaving either small slightly depressed ulcers with dense fibrous slightly raised edges, which contain a few amœbæ, or larger slightly depressed patches with smooth dense fibrous walls and adherent edges ; the true

nature of these might be difficult to recognise, but that more recent and typical ulcers are nearly always present in some part of the large bowel. Every stage from the small early ulcers through sloughing ones to chronic healed patches may be seen in the same bowel, for in the common relapsing type, if not efficiently treated, repeated attacks of ulceration may occur over a long series of years.

Distribution of the Lesions in the Large Bowel. The scattered nature of the amœbic ulceration with normal mucous membrane between them has already been sufficiently emphasised. In the acute type nearly the whole length of the large bowel is usually affected, but the ulceration is commonly more severe in the upper half, and if any part escapes it is generally the rectum and sigmoid. In chronic cases, in which death occurs directly from the primary disease, the lesions are also extensively distributed, but the individual ulcers are smaller and considerably less of the mucous membrane is involved. A third class of case is met with in the post-mortem room in patients who have died of amœbic liver abscess secondary to the bowel disease. If multiple small abscesses are present there will be extensive dysenteric lesions, often of a sloughing character, but if the typical large fibrous-walled amœbic liver abscess has been the cause of death it will be found that in about two-thirds of the cases only latent amœbic ulceration occurs; this is usually limited to the cæcum and ascending colon, and is commonly unaccompanied by recent dysenteric symptoms.

Complications. In the very acute type the extension of the inflammatory process to the outer coat of the large bowel often produces localised peritonitis over the greatly thickened and tender gut without any perforation, and it is very important to bear this in mind, as any surgical interference would remove the last chance of recovery which might take place through the specific medical treatment.

Perforation of the large bowel may occur in more chronic cases; this is most common in the cæcum or ascending colon, and gives rise to post-colic abscess liable to be mistaken for appendicitis. It may rarely occur in the lower part of the large gut, especially in the rectum, when general peritonitis usually results. The mucosa of the appendix may also be ulcerated occasionally in amœbic dysentery, but the ulceration yields to medical treatment with the rest of the bowel lesions.

Amœbic hepatitis, going on to liver abscess, if not detected early and efficiently treated, is by far the most frequent and important complication; it is dealt with in Chapter XII.

It is remarkable how rarely stricture of the large bowel results from the healing of extensive amœbic ulceration of the large intestine, no specimen being found in the Calcutta Pathological Museum among the large collection of nearly a century's experience of the premier hospital and medical school in India, and no record exists of its occurrence in over 6,000 post-mortems.

CLINICAL DESCRIPTION

The extreme variations in the lesions of the bowel produced by amœbic infection are naturally reflected in its very varying clinical course. This ranges from the most acute symptoms of sloughing and gangrenous dysentery down to those of chronic diarrhœa liable to be mistaken for tuberculous and other forms, greatly to the detriment of the patient, so the not infrequent absence of typical dysenteric symptoms should be strongly emphasised. The typical acute type will be described first, and subsequently the more variable chronic forms; but it should be borne in mind that chronic cases are always liable to undergo an acute exacerbation owing to the involvement of a fresh portion of the bowel wall by spread of the infection.

Gangrenous or Fulminant Type. This is the most acute type accompanied by very great thickening of the bowel wall with localised peritonitis over the inflamed patches and sloughing of the mucous membrane. It may come on rapidly, either as a first attack, or as an acute exacerbation of an antecedent dysentery. The patient will show a severe degree of prostration and toxæmia, and *will usually be passing* very numerous stools consisting largely or entirely of rosy mucus; black sloughs may be present, when the outlook will be very grave. The stools are very offensive, and often have a characteristic odour which can be recognised with experience but cannot be described. Fæcal matter may be entirely absent from the stools, when the outlook will be grave, as paralysis of the bowel wall may result from extensive destruction of the gut. On examining the abdomen, acute tenderness may be found over the site of greatly thickened patches of intestine, which may be palpable as tender masses. *Very copious hæmorrhage* is liable to occur in these cases, and may be the first indication of the severity of the ulceration and a warning of the necessity for active specific treatment.

Acute Type. The ordinary type of moderately acute dysentery forms a large proportion of the cases; this type is often difficult to differentiate from the bacillary form unless microscopical examinations of the stools are made for the causative *E. histolytica*, and for the characters of the cellular exudate of the mucus described later (p. 228). *In the absence of a proper diagnosis, correct treatment* cannot be given in the all-important early stages. The following clinical points may, however, help in the recognition of the disease.

Incubation Period. In water-borne acute infections in Chicago the incubation period was usually from eight to ten days. In mild and latent forms it is very variable.

The onset is commonly sudden, but with much less febrile and *constitutional disturbance than in the bacillary form*, even in serious cases. The remittent type of fever is comparatively rare and of bad prognostic import. Intermittent fever to only about 100° F. is more

frequent, but in about half the cases there is no rise of temperature, even in the acute stage, while fever is nearly always a much more marked feature of the bacillary disease. A rise of temperature later in the course of amœbic dysentery should always raise a suspicion of hepatic complication. In a majority of the cases the bowel symptoms come on acutely, but in a fair proportion the disease may begin with simple diarrhœa, with later development of typical dysenteric symptoms. Unless this is borne in mind the disease may not be recognised as amœbic at first, and valuable time may be lost before applying the proper treatment. Yet such cases may rapidly become very acute and even dangerous.

The number of the stools is very variable, but often ten to twenty may be passed in twenty-four hours, and in very acute cases they may be almost continuous. Straining and tenesmus is usually less than in the bacillary form, owing to the lowest portions of the large bowel being less frequently and extensively affected in amœbic disease. The character of the stools is seldom sufficiently distinctive to enable the form of the dysentery to be recognised by a naked-eye inspection, so it is most important to submit them to microscopical examination before commencing treatment whenever possible. When nothing but blood and mucus is being passed, the causative amœbæ can usually be found by the microscope in a few minutes, but more frequently the stools are mixed with fæcal matter, although rosy masses of mucus can usually be easily picked out for examination. In other cases blood-stained purulent matter is discharged containing the active amœbæ, and a peculiar characteristic odour is present, leaving little doubt in the mind of an experienced observer, although it is not safe to rely solely on such points if mistakes in diagnosis are to be avoided.

The appearances of washed dysenteric stools were described long ago by E. Goodeve in Calcutta. They afford valuable diagnostic and prognostic indications, and are obtained by pouring water on the whole stool and allowing it to stand for a short time to allow the mucus and sloughs to settle, when the surface water with most of the fæcal matter can be slowly decanted. Thus Goodeve described a brown or black slough, resembling a mass of old black cobweb, as evidence of very dangerous gangrene, but pus-infiltrated sloughs in a case of some days' duration as of good prognostic indication, gelatinous rosy mucus as an indication of an early stage of the disease, and abundant ropy mucus as an indication of approaching recovery. By examining washed stools daily the rapid decrease of the mucus in cases which are doing well under treatment with emetine can be noted, and in patients complaining only of diarrhœa the presence of a considerable amount of mucus will enable a correct diagnosis of dysentery to be made.

Microscopical Character of the Stools. The cellular content of the mucus of bacillary dysentery will be described later, on reference to which (p. 261) it will be seen that it differs much from the following

conditions met with in amœbic disease. The mucus resulting from the action of the *E. histolytica* shows comparatively few cells, apart from numerous red corpuscles which are often clumped together in the acute stages. Moreover, the large macrophage cells, so characteristic of bacillary dysentery, are rare or absent in amœbic disease; this is important, as they have often been mistaken for amœbæ, although this error should not arise if active living amœbæ are alone taken into account. Polymorphonuclear leucocytes are also fewer than in *bacillary disease; those that are present show degenerative changes,* including their nuclei, while they may number only about 7 per cent. of the total cells, the great majority being mononuclears; in all these points the cell exudate differs from that which is seen in bacillary dysentery. Charcot-Leyden crystals are also more frequently met with in the amœbic form. The great practical importance of the cytological changes in the mucous discharge is that they are easily detected by the simple microscopical examination of fresh mucus very early in the disease in the absence of laboratory facilities for making cultures of dysentery bacilli. The diagnosis can usually be made in this way a day or two before a cultural report is obtainable, and is often fairly certain even in cases in which the causative *E. histolytica* has not been found at the first examination.

The blood changes may also be of assistance. In amœbic disease there is commonly an increase of the leucocyte count, which may be as high as 30,000 in very acute cases. There is the same tendency as with the hepatic complications for the percentage of the polymorphonuclears not to be increased to nearly the same degree as in septic bacterial infections; this is a point in favour of a protozoal infection. In cases of long duration there is usually anæmia, when the form of relative leucocytosis described in amœbic hepatitis (p. 248) is commonly met with. In bacillary dysentery, on the other hand, leucocytosis is usually absent.

Abdominal Symptoms. There will be a variable amount of abdominal discomfort and pain, commonly referred to the navel. On palpation, tenderness, often accompanied by thickening of the bowel, will be noted, most frequently over the cæcum and ascending colon, and sometimes also over the sigmoid, but it may occur in any part, according to the main localisation of the lesions of the large bowel. The liver also may be enlarged and the lower edge tender during the frequent secondary inflammation of this organ. Care should be taken in abdominal palpation, as great thinning and weakening of the bowel wall may be present.

Chronic and Latent Amœbic Dysentery. At the opposite end of the pole to the fulminant is the chronic or latent variety, which is particularly liable to be wrongly diagnosed and treated, so it is of great practical importance. It may arise from the ordinary acute type passing into the chronic condition owing to the neglect of efficient [illegible]ent.

or it may be a mild infection from the first, without typical dysenteric symptoms, and only revealing itself in chronic diarrhœa, often alternating with periods of constipation. It is not sufficiently realised that many cases of amœbic ulceration of the large bowel produce diarrhœa without definite dysenteric symptoms, although careful and repeated examinations of the stools, and especially washing them in the way already described, will usually reveal the presence of mucus and lead to the discovery with the microscope of the causative *E. histolytica* and the typical cytological changes. How frequent such cases may be is shown by a Calcutta hospital series of post-mortems in fatal cases, for over one-sixth had been diagnosed during life as chronic or tuberculous diarrhœa and not recognised or treated as dysenteric. In another Calcutta series of 139 cases less than half presented dysenteric symptoms. It is this class of case which so frequently gives rise to the preventable amœbic hepatitis and liver abscess in the absence of the specific treatment for amœbiasis. It is shown later (p. 243) that during forty-nine years' records of the British Army in India, hepatitis was just as closely associated with diarrhœa as with dysentery; further, all three conditions decreased rapidly at the same time when the value of the emetine treatment came to be recognised.

In this class of case fever is completely absent as a rule. Careful examination of the abdomen usually reveals some thickening, with or without tenderness, of the large bowel; this is most frequently found in the right iliac fossa, and is only too often mistaken for appendicitis by those who have little or no tropical experience; sometimes it is even diagnosed as cancer of the cæcum, but it readily clears up under emetine, which reveals its true nature. Less frequently the lower portion of the large bowel is affected, giving rise to symptoms of tenesmus; the use of the proctoscope or sigmoidoscope will then allow the condition to be recognised; in these cases the number of stools will be greater and the diagnosis is easier. When only the *cæcum is involved there may be no diarrhœa.* These cases constitute the latent form so liable to be overlooked until the occurrence of an attack of secondary acute hepatitis leads to the detection of the primary bowel trouble.

Cirrhosis of the liver is also regarded by the writer as a common sequela of chronic amœbic dysentery, for he found the former disease to be five to seven times as frequent in Calcutta medical post-mortems as in London or Berlin, although alcohol could be excluded as its cause by the fact that cirrhosis was as frequent in abstaining Muslims as in the Hindus. Moreover, an elaborate study of some 5,000 post-mortem records showed active or healed lesions of dysentery, nearly always of the amœbic type, to be several times as frequent in cirrhosis as in the whole series of cases.

Complications. Localised peritonitis has already been mentioned (p. 225).

Post-colic abscess resulting from actual perforation of an amœbic ulcer most commonly occurs in the cæcal region, where it is liable to be mistaken for appendicitis or even for cancer of the bowel. In such active cases of amœbiasis *E. histolytica* can usually be found in the stools, and the specific treatment should first be used to cut short the pathological process. After this, if the swelling does not subside and abscess formation is suspected, an incision will have to be made, but it is remarkable that even large tumours of this nature will subside completely under emetine. Adhesions are usually formed, and these localise the collection of pus, but sometimes there is so much destruction of the bowel wall that resection of the cæcum may be required. Thus R. W. Runyan and A. R. Herrick have recorded four cases simulating cancer or tumour of the kidney in which they removed the cæcum with end-to-end anastomosis; three of the patients recovered. Perforation of the descending colon, sigmoid or rectum may lead to similar tumour-like masses in the left side of the abdomen, but they are comparatively rare, as general peritonitis is more likely to result from a perforation of the large bowel in this region. A. C. Reed and H. H. Anderson have recorded four cases in patients of from forty to forty-nine years of age in which cancer of the colon developed after amœbiasis lasting for from three to ten years.

Amœbic Granuloma or Amœboma are terms applied to tumour-like masses, usually in the neighbourhood of the cæcum. They may produce partial or complete obstruction of the large bowel and require active emetine treatment or even resection of the cæcum or colon.

Stenosis of the large bowel due to amœbic ulceration is very rare, but a case of rectal obstruction, relieved by emetine injections, is on record.

Pseudo-appendicitis. It will be well to emphasise once more the importance of not mistaking thickening of the cæcum in chronic and latent amœbic bowel affection for appendicitis. When this error in diagnosis is made the unfortunate patient is often subjected to a totally unnecessary operation, as not infrequently happens to those invalided to Great Britain after amœbic infections of the bowel. In this class of case the symptoms are very rarely of an urgent nature, so there is nothing to lose, but everything to gain, by giving a course of emetine injections for a week or so to patients coming from areas where amœbiasis is endemic before operating for suspected chronic appendicitis.

Sloughing of the skin after open operations for amœbic abscesses of the liver or post-colic abscesses used to be seen not infrequently before medical men began to realise the necessity of using the specific emetine treatment after opening such abscesses to destroy the causative organism. Extensive ulceration of the same nature may occur around the anus or in the form of fistulous or condylomatous-like ulcers in the perineum, on the buttocks, or even on the penis. The

sloughing may be of a phagedenic nature with necrosis of ribs and a fatal termination. Amœbæ may be found in the affected superficial tissues, but this condition is now less commonly seen, and it yields rapidly to emetine injections.

Cystitis and vaginitis due to *E. histolytica* have also been reported. Emetine clears them up.

Age Incidence. Amœbic dysentery is much less common in young children in most countries than the bacillary form, but in Egypt Perry and Bensted found seventy-three cases among 500 acute intestinal infections in children, 80 per cent. of whom were between the ages of one and five years.

DIAGNOSIS

From Bacillary Dysentery. In the tropical and subtropical zones the bacillary and protozoal forms of dysentery occur side by side and give rise to closely similar clinical conditions, but their treatment differs so completely that early and correct diagnosis is as important as it may be difficult without the routine use of the microscope. The rapid effect of emetine in the amœbic form is too often relied on as a diagnostic measure. Many mild cases of bacillary dysentery soon subside under the rest and purgative treatment which are commonly employed at the same time, and so the credit for the cure is wrongly attributed to the use of emetine. This is one reason why erroneous opinions are formed of the relative frequency of the two diseases. If the case is really one of amœbic dysentery little harm is done, but if emetine is relied on in a case of acute bacillary dysentery much damage may result owing to the neglect of the proper treatment in the early most amenable stage, and, in addition to this, the depressant effect of emetine may do actual harm. Moreover, once emetine has been administered the entamœbæ rapidly disappear from the stools in most cases, and the mistake can no longer easily be rectified by finding the causative protozoal organism. The microscopical examination of the mucus in a freshly-passed stool need not occupy more than a very few minutes, and it is just the acute types that are most likely to be mistaken for bacillary dysentery, and are most easily diagnosed by finding the *E. histolytica* and the typical cytological changes in the mucus. An early correct diagnosis is thus made, followed by the correct treatment. An enema of physiological salt solution at 37° C. may reveal floating specks of blood-stained mucus containing entamœbæ.

Clinically, a history of repeated relapses will be in favour of amœbic disease, as will be thickening of the cæcum and ascending colon, with tenderness due to localised peritonitis over the site of deep ulceration in acute cases. The occurrence of hepatitis or enlargement of the liver is also strongly in favour of amœbic infection.

A useful aid in diagnosis is the proctoscope or sigmoidoscope, both

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case which proved fatal after a week's emetine treatment, for in several places the whole of the *mucous and muscular coats had completely* disappeared, leaving only the peritoneal coat, which had given way in the cæcum with fatal results. Yet not a trace of the thickening due to the inflammatory infiltration of the bowel wall remained, but recovery was impossible owing to the irreparable destruction of the bowel wall.

Chronic cases of up to twenty years' duration have frequently lost all symptoms of dysentery in a few days under emetine, but, unfortunately, the immediate good results of the treatment are often followed at a later date by relapses. This is due to the drug failing to kill all the amœbic cysts within the bowel lumen, although the amœbæ in the bowel wall are destroyed ; this indicates the necessity of giving the specific drug orally as well as by injection. Moreover, the real efficacy of the drug in first attacks can only be ascertained in the endemic areas of the disease, for patients coming under treatment in Europe consist largely of the residual resistant relapsing cases invalided home on that account, whereas the very much larger proportion of patients who recover completely and permanently from a primary attack in the tropics naturally do not come under the observation of home workers. The proportion of relapses after efficient treatment in the tropics, apart from reinfections, is probably not more than 10 to 20 per cent., against a very much higher proportion among those sent home after a severe or relapsing attack. Thus in a military hospital in West Africa, Eldcot found that only 2 out of 82 early cases had to be invalided to Great Britain having failed to respond to injections of emetine and to orally administered emetine-bismuth-iodide and carbarsone.

A very high degree of leucocytosis, such as over 30,000, is of bad prognostic import. The severe hæmorrhages met with in deep amœbic ulceration yield rapidly to emetine and rarely prove fatal. Liver abscess complication used to be a serious cause of mortality, as many as 60–70 per cent. of these cases ended fatally, but the mortality has now been reduced to only about 2 per cent. in skilled hands by the method of treatment described under that complication (p. 250).

TREATMENT

Historical. It was only at the beginning of the present century that amœbic dysentery began to be differentiated from the bacillary form ; previously dysentery was treated as a single entity. Nevertheless, a perusal of the medical literature of the nineteenth century shows that ipecacuanha was extensively used and relied on in the treatment of dysentery in such tropical countries as India and parts of Africa, where we now know amœbic dysentery to be widely prevalent ; it was much less used in the temperate zone where the bacillary form prevails.

to allow the characters of any ulcer in the rectum or sigmoid to be noted, and also to enable swabs of mucus from the floors of the ulcers to be submitted to microscopical and bacteriological examination with considerably greater chance of detecting the specific organisms and cellular changes. Rounded raised ulcers with tawny yellow infiltration of their bases, nearly always containing active *E. histolytica*, and a surrounding congested ring, but with normal mucous membrane between the ulcers, are most characteristic of amœbic disease. The sigmoidoscope is not recommended, nor is it necessary, in acute cases; it is of great value in chronic forms of the disease.

X-ray examination after the administration of bismuth, preferably in an enema, may be of value in revealing the extent and distribution of the ulcerative lesions, as bismuth tends to adhere to the ulcerated surfaces and to show them up, but the interpretation of the photographs calls for considerable skill and experience.

The character of the stools is a very fallacious guide to diagnosis in most cases, but in the very acute type the presence of black sloughs is an indication of gangrenous amœbic dysentery, and a characteristic foul smell is of value to an experienced observer. The passage of pure blood or clots is more frequent in amœbic cases than in bacillary.

A Complement fixation test has been worked out by C. F. Craig with the use of an antigen of material obtained by prolonged culture of *E. histolytica*. In 91 per cent. of those giving a well-marked positive reaction amœbic infection was demonstrated, but in only 1 per cent. of the controls. H. E. Meleny and W. W. Frye obtained positive results in animals parenterally inoculated with *E. histolytica* provided that a tissue invasion by the organism resulted. Negative results are also said to be of value as an indication of cure. The technique is difficult and requires a good laboratory. Some workers have found this test unreliable, and in one instance tests at two laboratories on the same cases gave a number of contradictory findings.

Prognosis. In pre-emetine days neglected cases of amœbic dysentery, so often seen in the indigenous races coming to hospital in the tropics, often resulted in death; in them the mortality varied between 20 and 40 per cent. At the present time, however, recovery as regards the immediate attack nearly invariably takes place unless in cases of the very acute fulminant type with gangrene of the mucous membrane or peritonitis, or with extensive post-colic abscess due to sloughing of the whole thickness of the bowel wall. Moreover, rapid improvement in a grave case may be followed by death a few days later from the perforation owing to the ulceration having produced destruction of the whole thickness of the bowel wall except the thin peritoneal coat, which subsequently gives way. The remarkable effect of emetine in removing all the gelatinous infiltration of the bowel wall within a few days is well illustrated by a plate in *Bowel Diseases in the Tropics*, showing the post-mortem appearance in a very severe

evening, last thing at night, after the patient is in bed. In addition, either 20 minims of Tr. opii is given half an hour before the dose, or more simply the Madras method of giving 10 grains of tannic acid with 20–30 grains of ipecacuanha powder in cachets or with a drachm of mucilage in 1 oz. of water may be used with advantage, as this *precipitates the alkaloid in the stomach and it is redissolved in the* small bowel. The tannic acid also inhibits the formation of mucus, which may form the bulk of the vomited matter. The powder may also be given in keratine-coated pills or in cachets, but it is rather bulky, so some prefer to give 1 grain of emetine hydrochloride when oral administration is indicated.

Dosage. It is important to remember that emetine is a cumulative drug, and, when continued too long without a break, it is liable to produce troublesome paralysis of various muscles, usually those of the arms and legs. Vitamin B_1 in 10 mg. doses daily has been reported to be of value in the treatment of such paralysis, and also as a preventive in patients showing intolerance to emetine. The maximum total quantity in a course of treatment should, therefore, not exceed 12 grains as a rule, and never more than 15 grains unless in a case of great urgency. Such cases are very rare, as the drug has a very rapid action and a course of 8 grains is usually sufficient to clear up all the symptoms. After an interval of two or three weeks a shorter course may be given if required. The usual daily dose is 1 grain in 1 c.c. of water intramuscularly or subcutaneously ; the injections are given in different sites, as they produce a good deal of pain in some persons, but the drug can usually be injected alternately in the deltoid regions without much inconvenience. In very acute or fulminant cases in which there is no time to lose, 1 grain may be injected slowly intravenously for the first day or two until the crisis is past, but this is not often required. In severe cases it is often of advantage to give a dose morning and evening, and for the first two or three days a total of 1·5 or even 2 grains a day may be given, especially if the patient weighs 12 stone or over. Body-weight and general health must be taken into account ; a course of 12 grains may be far too much for a light debilitated female. A. C. Read advises that the total amount of emetine in one course should not exceed 0·01 gm. per kilo body-weight. If the case is one of uncomplicated amœbic dysentery great relief and reduction of the number of stools may be obtained within twenty-four hours, and in two or three days the patient will be very much better and out of danger, provided no irreparable damage has been done to the bowel by the disease before the patient comes under treatment. In children of eight years ⅓ grain, and in quite young children ⅛ grain, may be given.

In addition to injections of emetine, it is most important to administer either the same drug in 0·5 to 1 grain doses, or powdered ipecacuanha in 20–30 grain doses last thing at night for a few days

Soon after the writer, in 1902, showed amœbic dysentery to be very common in Calcutta, he came to the conclusion that ipecacuanha was a *specific in both* amœbic dysentery and amœbic hepatitis, but useless in bacillary dysentery ; in 1912 he discovered the still greater value of emetine. Ipecacuanha itself had been brought to Europe from Brazil in 1658, and was used in dysentery in India as early as 1660, but for years it was given in comparatively small doses. E. Parkes appears to have been the first to give full doses of 30–60 grains as early as 1846, although Docker has sometimes been credited with this advance in 1858 in Mauritius. As early as 1886, both Norman Chevers and Maclean advocated the drug in hepatitis as a preventive of liver abscess, but strange to say, this important observation was largely forgotten a decade or two later until the method was put on a scientific basis by the establishment of the fact that this serious liver affection is invariably a secondary complication of the newly-differentiated amœbic dysentery. Emetine itself was isolated by Pelletier from ipecacuanha as early as 1817, but in spite of one or two abortive attempts to use it in dysentery it was not until 1912 that L. Rogers proved its immense value in amœbic affection of both the bowel and the liver. Since then new compounds of emetine have been introduced for the treatment of resistant relapsing cases.

Specific Treatment with Ipecacuanha and Emetine. Proof is now available that injections of emetine hydrochloride can destroy all the living amœbæ both in the innumerable small amœbic liver abscesses and in large single ones. Emetine is therefore one of the most definitely specific drugs known. Its lethal action on non-pathogenic amœbæ was first established by E. B. Vedder in 1911, but its power to kill *E. histolytica in vitro* was long disputed on account of the fact that this protozoon soon dies after being expelled from the human or animal body, but with the discovery of methods of cultivating the organism, C. A. Kofoid and E. H. Wagener showed that emetine hydrochloride in dilutions of 1 to 10,000 kills the *E. histolytica* in twenty-four hours. Unfortunately, the encysted stage is much more resistant to all drugs, and so is very difficult of elimination from the lumen of the bowel ; hence the number of relapses in chronic amœbic dysentery.

Ipecacuanha contains in addition to emetine a closely allied alkaloid, cephæline, which has a definite but less powerful action than emetine in amœbic dysentery, so that the combination of the two in ipecacuanha powder is of considerable value, but no less than 90 grains of ipecacuanha is required to furnish 1 grain of emetine, which is the usual dose of the latter when given intramuscularly. Emetine is therefore far more convenient to use ; it does not suffer from the drawback of causing vomiting as is so commonly the case when powdered ipecacuanha is given by the mouth. Special precautions are necessary in the use of ipecacuanha orally, including giving the powder on an empty stomach three hours after a light meal, preferably in the

doses of 0·5 gm. thrice daily for ten days : in these doses it causes a profuse but painless watery diarrhœa in some patients so that it is safer to begin with doses of 0·25 gm. twice daily and go on to the larger doses if the drug is well tolerated.

It is not toxic and does not necessitate rest in bed or special restrictions in the diet. The drug can also be given by rectal injections, 200 c.c. of a 2½ per cent. solution after washing out the bowel with an alkaline enema. The injections are given once daily for ten days, preferably at the same time as the oral course of treatment, and are retained by the patient as long as possible. The treatment is worth trying in the intervals between courses of emetine.

Vioform is a somewhat similar drug ; A. C. Read in California recommends it in preference to chiniofon, he gives 0·25 gm. capsules thrice daily for ten days and a second similar course after a week's rest.

Acetarsone tablets, orally, are said by C. F. Craig to have cleared up some resistant carriers after one or two courses of the drug.

The old Indian remedy, **Kurchi bark**, has been investigated in the Calcutta School of Tropical Medicine. Acton and Chopra advise the oral use of Kurchi Bismuthous Iodide in 10-grain doses twice daily for ten or more days taken half an hour after 60 grains of sodium bicarbonate and 40 grains of sodium citrate. Naidu has reported two fatalities in children due to the use of kurchi bark.

Sulphonamides do not inhibit the growth of *E. histolytica* in cultures and so are unlikely to be of any value in amœbiasis unless there is also a bacillary infection.

Antibiotics. At the present time many antibiotics are undergoing trial—especially aureomycin and terramycin. Several observers report rapid improvement in the clinical condition with disappearance of the entamœbæ from the stools but in some of the reports the relapse rate has been high. The dosage recommended varies greatly, ranging from 1 to 4 grams daily in divided doses. The total dosage given varies from 10 to 30 grams. These drugs are very expensive and in large doses are likely to cause symptoms of ariboflavinosis, so that simultaneous treatment with vitamin B complex is desirable. For the present it would seem advisable to use antibiotics as adjuvants to the standard emetine treatment rather than as substitutes. They may be used with most advantage in severe primary cases.

General treatment includes rest in bed and fluid diet in the acute stages, and milk should be citrated to prevent the formation of coagulated masses. During convalescence great care should be taken for a considerable time to avoid indigestible or irritating foods, including pastry, cheese and alcohol. Many patients in the tropics suffer from malnutrition which predisposes to the disease. A generous diet containing plenty of vitamins should, therefore, be given as soon as it can be digested.

As ipecacuanha and emetine are themselves laxative, purgatives

after the completion of the course of injections, or 0·5 grain of emetine may be given orally in addition to the 1-grain injections if preferred. The object of this is to destroy the parasites within the lumen of the bowel before they have had time to reach the resistant encysted stage, in addition to killing off those in the diseased tissues in the bowel wall *itself.* Subsequent relapses are often due to the common neglect of this essential precaution, and it is especially necessary in cases coming under observation during a relapse. Such full doses of ipecacuanha can usually be given without sickness, and with very little nausea if administered immediately after a course of emetine injections. In ordinary cases, 1-grain injections of emetine daily for a week, followed by full doses of ipecacuanha every night for another week, suffice to clear up the disease, and convalescence is rapid as a rule. Repeated stool examinations should be made, if possible, for several weeks, and if this is impracticable it is a good practice to give a second course of injections a fortnight or so after the end of the first course.

In relapsing cases a similar course of treatment should be given, but in the resistant cases most commonly seen in patients invalided home from the tropics more drastic treatment may be required. For this purpose *emetine bismuth iodide* in 3-grain doses daily by the mouth in soft gelatine capsules for twelve consecutive days should be administered after a course of emetine hydrochloride intramuscularly, in order to destroy the cysts within the bowel contents. The drug causes great nausea and severe diarrhœa, but several observers have reported the elimination of the cysts from the stools in from 80 to 90 per cent. of cases. It is possible that the rather violent purgative action of the drug is an important factor in getting rid of the infection.

Diodoquin is advised in latent cases and carriers by C. F. Craig in 0·21 gm. tablets, seven to ten daily for twenty days.

Carbarsone, 4-carbamino-phenyl-arsenic acid, containing 28·8 per cent. of arsenic appears to have the great advantage of being effective in amœbic disease without being toxic. A. C. Read advises 0·25 gm. twice daily for ten days in gelatine capsules orally, or a total course of 75 mg. per kilo of body-weight spread over at least ten days, but he does not recommend it in amœbic hepatitis. He obtained 90 per cent. of cures in cases followed up for eighteen months. It can also be given in 200 c.c. enemas of a 1 per cent. solution with 2 per cent. sodium bicarbonate last thing at night after a sedative of sodium amytal, and this method proved effective in some cases after the failure of oral administration. Moreover, in carriers the cysts may disappear from the stools in three days.

Chiniofon is identical with Yatren (Bayer). It contains a considerable proportion of iodine in a combined form and has been widely used, chiefly by continental physicians. Like the other subsidiary drugs, it cannot take the place of emetine, the action being chiefly on entamœbæ which are free in the intestinal contents. By the m

CHAPTER XII

AMŒBIC HEPATITIS AND LIVER ABSCESS

The most frequent and serious complication of intestinal amœbiasis is secondary infection of the liver, which goes on to abscess formation if not recognised and effectively treated in good time. In the decade ending in 1906 liver abscess was only second to typhoid fever as a cause of mortality in the British Army in India, with nearly 100 deaths a year, and one case to every eight of dysentery. Now it is an easily preventable disease in those who come early under skilled treatment, and the case mortality of already formed liver abscess has been reduced from about 40 to 60 per cent. to 2 to 4 per cent. when modern treatment is carried out by men of experience. A brief history of how this revolution has been brought about will serve best to bring out the scientific basis of our present knowledge of the subject.

Historical. Up to as late as 1902 the ætiology of tropical liver abscess was unsettled, and in opening a discussion on the subject A. Duncan, with long Indian experience, concluded that while the rare multiple small liver abscesses were related to dysentery, the large single tropical form was not. Amœbic dysentery was not up till then known to occur in India, and was not admitted to be a distinct disease or described separately in the leading work on tropical medicine; even bacillary dysentery was only beginning to be recognised as a specific disease. In the same year L. Rogers established the following essential facts as the result of two years' researches in Calcutta. Previously amœbæ had been found in less than half of two small series of liver abscesses, and were not recognised as the cause of the condition, but Rogers showed that by examining scrapings from the wall of such abscesses, either post-mortem or when they were opened, living amœbæ could be demonstrated in every one of nearly three-score cases. He also found that over 80 per cent. were sterile as regards the septic organisms of ordinary suppuration. Moreover, in a large series of his cases there was either clinical or post-mortem evidence pointing to the existence of antecedent dysentery in 90 per cent. of the cases, and in a later series in 98 per cent. Also, the dysentery was always of the amœbic variety which was found to be the most common form in Calcutta autopsies. Actual dysenteric symptoms were rarely present in the patients who were admitted for liver abscess, and in 20 per cent. no history of previous dysentery could be obtained, but in post-mortem examinations of such cases a few latent amœbic ulcers were almost invariably found; they were usually limited to the cæcum and ascending colon and produced no bowel symptoms. It was thus clear that large tropical liver abscess was always secondary to amœbic ulceration of the large bowel, often latent in character, so that the amœbæ, and not septic

are not required except for a preliminary emptying of the bowels. In severe acute cases enemata are to be avoided on account of the possibility of deep ulceration being present, for they have been known to have caused fatal perforation of the bowel wall.

Surgical treatment is very rarely required as it is harmful in the early acute stages, and under the treatment now available continued dysenteric symptoms lasting for long periods are rarely seen, in spite of the frequency of relapses which yield to a further course of the specific treatment. In cases coming under observation too late to avert the formation of a post-colic abscess in the right iliac fossa, the pus may require to be drained if resolution does not take place under emetine; resection of the cæcum may be needed if much of its wall has been completely destroyed. Ulcers of the appendix nearly always heal under emetine.

LEONARD ROGERS

hepatitis as a preventive of liver abscess on empirical grounds, but had nearly gone out of use in India by 1900.

Recognition of the Presuppurative Stage of Amœbic Hepatitis. Three decades ago the almost invariable history of a liver abscess patient was that he had suffered from fever of an obscure nature lasting several weeks, or even two to three months, for which he received quinine, or if hepatitis was suspected, ammonium chloride; after being a month or two in hospital, liver abscess was found by aspiration and the abscess opened, usually with a fatal result (*see* Fig. 41). The writer when investigating the blood changes in fevers in Calcutta, met with

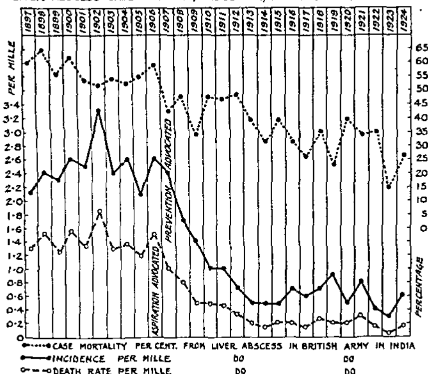


FIG 43. Chart showing reduction of liver abscess cases in British Army in India under ipecacuanha and emetine treatment.

a number of such cases, in not one of which had a single grain of ipecacuanha been given, and in 1905 he pointed out that they could be distinguished by the occurrence of a leucocytosis which had the peculiar feature that there was often little or no increase in the proportion of the polymorphonuclears, and he found that every one of sixteen cases with a count of over 12,000 leucocytes went on to liver abscess formation under the ammonium chloride or quinine treatment then used. In 1907 the writer recorded a series of fifteen cases of obscure fever lasting for anything up to fifty-three days; some of these had a history of dysentery, others had none; some had symptoms of hepatitis, others had no such symptoms, but all had leucocytosis or

organisms, were the cause of the abscesses. The extreme rarity of liver abscess in the temperate zone was due to the infrequent occurrence of amœbic dysentery there, as the bacillary form does not give rise to liver abscess. In cases in which multiple small liver abscesses were found post-mortem active amœbic dysentery was always present; even in the smallest pinhead-sized abscesses there were only amœbæ, and

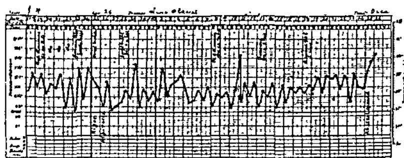


FIG. 41. *Temperature chart of amœbic fever going to liver abscess.*

no bacteria, so that the amœba was obviously the primary cause of the condition.

The establishment of these facts also led L. Rogers to suggest as early as 1902 that liver abscesses due to an amœba might prove to be amenable to some less dangerous form of treatment than the usual open operation, which was almost inevitably followed by secondary

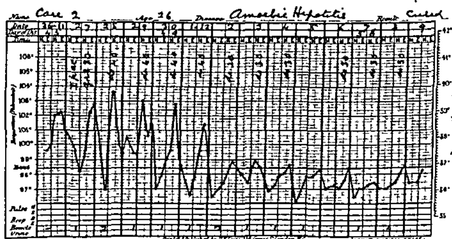


FIG. 42. Temperature chart of amœbic fever treated with ipecacuanha.

septic infection in a damp tropical climate. Among a large series of cases in which the abscess was sterile when first opened he never found one to remain so for more than a very few days after the open operation with drainage. He therefore advised repeated aspirations and injection of quinine solutions, together with the oral administration of large doses of ipecacuanha. The use of ipecacuanha had already been advocated in 1886 by Norman Chevers and Maclean in cases of

Acute Form. In this class the patient has high fever and an enlarged and tender liver ; there is usually a history of recent dysentery or diarrhœa, which may or may not have ceased before his coming under observation. The temperature curve is of an irregular remittent type, profuse perspiration being followed by a decline. The liver will be enlarged and tender, reaching well below the costal margin, or it may be enlarged upwards, producing deficient breathing at the right base ; in this case X-rays will reveal a fixed and elevated right dome of the diaphragm, or of the left dome in the rare cases of left lobe inflammation. A shadow may be seen in the contiguous base of the lung when the inflammation spreads through the diaphragm ; this shadow does not necessarily indicate that suppuration has occurred, for it may yield readily to emetine. Palpation of the abdomen is likely to show some tenderness and thickening over the cæcum and ascending colon, and occasionally over other parts of the large bowel, indicating the presence of amœbic ulceration. A blood examination will reveal leucocytosis, which may be anything up to 30,000, or in rare cases higher still. In the acute type the proportion of polymorphonuclears is usually between 80 and 90 per cent., but never over the latter figure. In these acute cases the liver is very congested and puncture may be followed by fatal intra-abdominal hæmorrhage ; four such cases were courageously published by Hatch in India, in none of which was an actual abscess found post-mortem. In the most acute type it is impossible to tell on clinical grounds whether multiple small liver abscesses are present or not. As the treatment is the same in either case this is of no consequence, but multiple abscesses are more likely to have occurred if acute sloughing dysentery is also present with great inflammatory thickening of the large bowel ; this is indicated by the presence of tender sausage-shaped masses in the abdomen.

Chronic Form. This also commences with fever, which is often the only symptom for weeks, and the discovery of the true nature of the case usually depends on a blood examination revealing a moderate degree of leucocytosis, often with little or no increase in the proportion of the polymorphonuclears. J. Heatly-Spencer has drawn attention to the presence of the Schilling-Torgau modification of the Arneth index, shown by a shift to the left with a rise in the band-form granular cells and a fall of the lymphocytes. Successful emetine treatment results in a reversion to a normal differential leucocyte count. These findings show the need for an inquiry into a history of previous dysentery or diarrhœa, for forty-nine years' record of the British Army in India show that the relationship between diarrhœa and liver abscess is just as close as that with dysentery, and many chronic cases of amœbic colitis show only chronic diarrhœa, often mistaken for the tuberculous form. Repeated examinations of the stools for *Entamœba histolytica* should be made in all forms of hepatitis, as a positive result will be of great value. Some enlargement of the liver is generally present, but

a relative increase of the leucocytes in proportion to the red corpuscles; in all of these cases the temperature fell to normal and all the symptoms cleared up in two to six days on large oral doses of ipecacuanha, and liver abscess formation was thus averted (*see* Fig. 42).

Rationale and Results of Ipecacuanha and Emetine Treatment. The scientific data on which the success of the previously discarded empirical treatment is based are, firstly, the fact already mentioned that in fatal liver abscess cases latent amœbic ulceration occurs in the upper part of the large bowel, and, secondly, the discovery that ipecacuanha is a specific in amœbic dysentery only, and would therefore clear up the latent amœbic infection of the bowel on which the hepatitis is dependent. It is essential that the drug should be administered during the pre-suppurative stage and that a correct diagnosis should be made by means of the blood changes in this early period of the disease. Amœbic liver abscess was thus shown to be an easily preventable disease, as is now generally recognised. With the introduction of emetine in 1912 still better results were obtained, and the incidence per mille of liver abscess in the British Army in India in 1897–1906 of 2·50 per mille had fallen in 1920–26 to 0·51 per mille, a reduction of 79 per cent. Further, the ratio of liver abscess cases to dysentery cases, which was 1 to 8 in 1898–1911, had fallen to 1 to 29 in 1912–19, or a reduction of 73 per cent. (*see* Fig. 43). In 1928 to 1935 there were only six deaths in eight years. The rate per mille worked out at one-hundredth part of that of the decade 1897–1906 before the establishment of the modern method of treatment. Very similar results have been reported from French Indo-China by P. Huard, where the records indicate that in early days, when dysentery was treated with ipecacuanha, abscess of the liver was uncommon, but it became alarmingly fatal from 1903 to 1911, when beta-naphthol and other drugs had largely replaced ipecacuanha; subsequently to the emetine treatment of dysentery being introduced in 1912 hepatic abscess again became very rare. Yet as late as 1942 C. J. Berne recorded that in a U.S.A. hospital the old surgical treatment of 74 cases of amœbic liver abscesses showed a case mortality of 85 per cent.

PRE-SUPPURATIVE AMŒBIC HEPATITIS

The period of prolonged fever due to amœbic infection of the liver prior to actual abscess formation has been termed pre-suppurative by the writer. The importance of recognising the disease in this easily curable stage in order to prevent it from going on to the more dangerous liver abscess can hardly be exaggerated. The diagnosis is by no means always easy in the more chronic and insidious types, between which and the readily recognised very acute cases there is every gradation, so the latter may with advantage be described first.

Acute Form. In this class the patient has high fever and an enlarged and tender liver ; there is usually a history of recent dysentery or diarrhœa, which may or may not have ceased before his coming under observation. The temperature curve is of an irregular remittent type, profuse perspiration being followed by a decline. The liver will be enlarged and tender, reaching well below the costal margin, or it may be enlarged upwards, producing deficient breathing at the right base ; in this case X-rays will reveal a fixed and elevated right dome of the diaphragm, or of the left dome in the rare cases of left lobe inflammation. A shadow may be seen in the contiguous base of the lung when the inflammation spreads through the diaphragm ; this shadow does not necessarily indicate that suppuration has occurred, for it may yield readily to emetine. Palpation of the abdomen is likely to show some tenderness and thickening over the cæcum and ascending colon, and occasionally over other parts of the large bowel, indicating the presence of amœbic ulceration. A blood examination will reveal leucocytosis, which may be anything up to 30,000, or in rare cases higher still. In the acute type the proportion of polymorphonuclears is usually between 80 and 90 per cent., but never over the latter figure. In these acute cases the liver is very congested and puncture may be followed by fatal intra-abdominal hæmorrhage ; four such cases were courageously published by Hatch in India, in none of which was an actual abscess found post-mortem. In the most acute type it is impossible to tell on clinical grounds whether multiple small liver abscesses are present or not. As the treatment is the same in either case this is of no consequence, but multiple abscesses are more likely to have occurred if acute sloughing dysentery is also present with great inflammatory thickening of the large bowel ; this is indicated by the presence of tender sausage-shaped masses in the abdomen.

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entamœbæ from the stools. Sometimes there are no definite signs of liver involvement ; in such cases the results of a short course of emetine treatment are so striking that there can be little doubt of the nature of the disease. For these cases the term hepatic amœbiasis would be more appropriate than amœbic hepatitis, which conveys the suggestion that the condition is necessarily associated with the obvious manifestations of hepatitis.

Treatment

The treatment of this stage is as simple as it is satisfactory, especially since the introduction of injections of 1-grain doses of emetine hydrochloride, which are each equivalent to 90 grains of the nauseating powdered ipecacuanha. Generally 1 grain daily is sufficient, but in patients weighing 12 stone or so more may be necessary, such as $\frac{3}{4}$ to 1 grain morning and evening. The temperature should fall to normal within a week, and enlargement of the liver and leucocytosis may subside greatly within the same time ; in some cases it is necessary to continue the treatment longer, but it is rarely advisable to give a total of more than 12 grains in one course for fear of toxic symptoms in the form of paralysis, as the drug is cumulative, but after two weeks' interval a further course may be given. In the case of patients who *are less than 8 stone in weight, it is not advisable to give more than 8* grains in one course. To avoid the danger of relapse either full doses of ipecacuanha or of emetine should be given orally for another week to eliminate infection from the interior of the bowel, as described under the treatment of the intestinal affection. The disappearance of leucocytosis, in addition to the cessation of fever, is the best sign of success in averting abscess formation, but if either or both continue it is probable that suppuration has taken place, and the treatment advised later for liver abscess must be carried out. In a case of hepatitis which is in any degree acute, aspiration should on no account be performed until a course of emetine injections has been given to remove the dangerous congestion, which might lead to intraperitoneal hæmorrhage after such operative interference. The manner in which acute pain and tenderness of the liver are relieved, and the organ becomes reduced by 2 or 3 inches in size with loss of fever, all within three or four days under this treatment, is one of the most remarkable occurrences in medicine. In chronic cases recovery, though less dramatic, is usually quite satisfactory. All alcohol should be avoided in treatment and during convalescence, which is often surprisingly rapid. Any thickening of the large bowel may also disappear during the treatment, owing to healing of latent ulcers. It is noteworthy that various observers have found that yatren, kurchi, stovarsol, and even emetine bismuth iodide, failed to avert the formation of liver abscess in the way that emetine so effectually does, so the latter is clearly the most specific treatment, in amœbic hepatitis at any rate.

the patient often does not complain of pain in the hepatic area, and tenderness may be absent. In such cases the effect of emetine treatment in rapidly stopping the fever, removing the leucocytosis and restoring health confirms the diagnosis of amœbic disease. X-rays may often help by showing diminution or loss of the movement of the right side of the diaphragm. These insidious cases are likely to be overlooked until liver abcess has developed unless amœbic hepatitis is always kept in mind in cases of obscure fever and complete routine blood examinations are made. The chronic cases shade off into more easily-recognised subacute ones with definite hepatic symptons.

In cases of doubt there need be no hesitation in giving emetine as a diagnostic agent ; there are many instances on record in which an obscure fever with slight leucocytosis has yielded promptly to a few doses of emetine after having resisted all other forms of treatment for weeks.

Duration of the Pre-suppurative Stage. In a series of cases of liver abscess in Europeans in Calcutta the duration of the fever before an abscess was found was over two weeks in 84 per cent. and over a month in 50 per cent., while in fifty-three Indian patients the figures were 97 and 89 per cent. respectively. There is thus ample time to detect the disease in the pre-suppurative stage, and the formation of a large amœbic liver abscess is easily preventable in patients who come fairly early under skilled treatment, and there is clear evidence that the establishment of the diagnostic value of the blood changes, together with the effectiveness of the specific treatment with ipecacuanha and emetine has already greatly reduced the prevalence of this serious disease in India and elsewhere, as proved by the figures of the British Army in India already given (*see* Fig. 43, p. 241).

Differential Diagnosis. In warm climates where amœbic disease of the bowel is endemic, hepatitis is nearly always secondary to that affection. Alcoholism strongly predisposes to amœbic hepatitis, although the disease may occur in total abstainers. The excessive use of alcohol in warm countries tends to produce congestion of the liver, which might be confused with amœbic infection of the liver, but it is not usually accompanied by leucocytosis. A somewhat similar condition has been described under the name of " tropical liver," and ammonium chloride has been recommended in its treatment if there is no history of dysentery ; but the writer has seen so many liver conditions develop into liver abscess while under treatment with that drug that he holds that ammonium chloride should never be employed for " liver " until chronic amœbic hepatitis has been excluded, even when there is no history of bowel trouble. Every case of hepatitis or hepatic congestion should be assumed to be amœbic in nature unless there is clear evidence that some other cause exists. Unexplained fever with leucocytosis of the characteristic type should be suspected to be due to amœbiasis, even in the absence of a history of dysentery and of

explanation is that during the course of long-continued passage of the amœbæ to the liver, most of these undergo degeneration within clots in the portal radicles and fail to get through the walls of the vessels and so start breaking down the liver tissue ; but sooner or later localised clotting takes place which is of sufficient extent to produce focal necrosis and escape of the protozoa into the liver tissues ; then spread takes place as in the acute form just described until a reactionary fibrous wall is formed, and a single large localised abscess results.

Predisposing Causes. An analysis of nearly 400 liver abscess cases in Calcutta showed that 70 per cent. occurred between the ages of twenty-one to forty years, about 5 per cent. only below twenty, and the same proportion over fifty, while the disease is extremely rare below the age of ten years with only two cases. The figures were nearly the same for Europeans and Indians, and all races are affected. Males show a remarkable preponderance with 97·3 per cent. among Indians and 95·6 per cent. in Europeans. One of the causes of this is the strong predisposing effect of alcohol, which is consumed more freely by males, especially among Indians, but liver abscess may occur in abstainers. Females are, perhaps, less liable to amœbic dysentery through staying more at home, but there are no reliable statistics to show the relative frequency of the disease in females as compared with males, owing to the smaller number of European females in the tropics, while few Indian females come into hospitals. In Korea, however, 9·16 per cent. of Ludlow's 240 cases were in females. He also lays stress on alcohol as a predisposing cause.

Varieties and Distribution of Large Amœbic Abscesses

In 70 per cent. of the Calcutta cases the typical large amœbic liver abscesses were *single, and in the remainder from two to four* were present, in half of which there were only two, exclusive of multiple small abscesses which are not recognisable clinically during life. Of the single abscesses only 16 per cent. were in the left lobe on account of its much smaller size. The left lobe abscesses for the same reason more frequently involve surrounding structures, and may open into the base of the left lung, less commonly into the pericardium or the stomach and very rarely into the lesser sac of the peritoneum. They also soon become adherent to the anterior abdominal wall and may assume an *hour-glass form by escape of some of the* pus into the superficial tissues, or they may form the so-called supra- or sub-hepatic abscesses through escape of some of the pus through the liver capsule into surrounding tissues on the upper or lower surface of the lobe. This may also be the case with right lobe abscesses, especially those on the upper surface of the liver, and in no less than twenty-six of eighty-one fatal right lobe cases in Calcutta a secondary abscess was found in the lung post-mortem. Some have thought that suppuration may commence between the diaphragm and the liver or in the base of the

SUPPURATIVE AMŒBIC HEPATITIS, OR TROPICAL LIVER ABSCESS

Ætiology and Pathology. Tropical liver abscess need only occur in cases in which the patient comes under observation too late for the disease to be *efficiently treated in the pre-suppurative stage* ; *it* is always preventable if a correct diagnosis has been made and the specific curative treatment used in the early stage. Its ætiology is therefore the same as that already described, only it is very important to bear in mind that between 80 and 90 per cent. at least of the cases are quite free from secondary bacterial infection, and so do not require the same treatment as septic abscesses. They are always primarily due to the *E. histolytica* gaining entrance to the radicles of the portal system in the infected submucous coat of the large bowel and passing to the liver through the portal system. In Indo-China secondary bacterial infections of amœbic liver abscesses appear to be more frequent than in India ; they are attended by a much higher mortality.

Mode of Formation. In the very numerous minute liver abscesses found post-mortem in cases of active sloughing amœbic dysentery the amœbæ are found in the earliest stage of pinhead-sized lesions within the radicles of the portal vein of the liver ; these are often entangled in blood clot, where some of them undergo degenerative changes. Acute congestion of the liver is thus produced, with breaking down at numerous points to form abscesses up to an inch or so in diameter, formerly they were mistaken for septic pylephlebitis until L. Rogers, in 1903, described and illustrated their production by the amœbæ alone. The formation of single or multiple (up to four) large separate liver abscesses surrounded by dense fibrous walls, which constitute the clinical tropical liver abscess, is not so easy to account for as being due to portal infection from the bowel, but Rogers has given the following explanation. Light is thrown on the process by the occurrence of a somewhat rare intermediate class of cases in which there is a rapid formation of large ragged-walled, very acute amœbic abscesses, around which are seen a number of small suppurating points. Sections through the wall show that the latter are formed by the inflammatory process spreading along the veins from the main cavity, and by this means concentric circles of the liver substance are successively broken down, and the abscess enlarges in this manner until, if the patient survives long enough, an inflammatory reaction produces the formation of the *limiting fibrous wall which is seen in the typical* more chronic abscess. Subsequently the abscess increases in size by expansion, but without further destruction of the liver substance ; in this way there may be the formation of a cavity containing even six or more pints of pus without much constitutional disturbance or a dangerous degree of damage to the liver tissues. The difficulty is to explain how a single large abscess originates, but the simplest

to one of well over 10,000 in a normal red count. For example, in a case in which only 7,500 white corpuscles were found the reds numbered only 2,500,000, so that the proportion of white to red was similar to a count of 15,000 white to the normal 5,000,000 red ; in this case a large liver abscess was found post-mortem.

Great enlargement of the liver is in favour of abscess formation, yet an extremely tender liver extending three or more finger-breadths below the costal margin in the nipple line may still be in the pre-suppurative stage and, if so, will rapidly subside in a few days with emetine treatment. Loss of movement of the one side of the diaphragm, and even a shadow at the base of the right lung, may be present, and yet the disease may yield to medical treatment. Radiography therefore gives little help in determining whether an abscess has actually formed or not, as suppuration does not produce recognisable increased density of the organ, but X-rays may occasionally be of use in indicating the extension of an abscess to surrounding tissues such as the lung. Cameron and Lawler advise replacement by air of half the amount of pus evacuated by aspiration and subsequent X-ray examinations in both the recumbent and the erect positions to determine the shrinkage of the abscess cavity. In Indo-China Huard has found injections into abscess of the liver of lipiodol, collargol or tenebryl of value in allowing of their ramifications to be observed by radiological examinations.

Localised tenderness on pressure often furnishes an indication of the probable site of suppuration, and so should be sought for with care before an exploratory puncture is made. A. L. Ludlow, in Korea, noted that deep-seated pain, elicited by a sudden thrust with the end of a finger, is an important and practically constant sign of liver abscess. If there is also local œdema of the chest or abdominal wall over the enlarged liver the probability of pus being present is greatly enhanced. Left lobe abscesses most frequently come to the surface in the epigastrium, and fluctuation may be present ; such cases have been mistaken for superficial abscesses of the abdominal wall on account of the small degree of constitutional disturbance which may be associated with them.

Jaundice is usually completely absent, but in one Calcutta case, with well-marked jaundice, an abscess pressing on the cystic and common bile ducts was correctly diagnosed. Copious sweats may occur in the pre-suppurative stage.

Amœbic abscess of the lung secondary to that in the liver may be so insidious that the first definite symptom may be that the patient coughs up copious blood-stained sputum with little or no odour ; this symptom may continue for months, and has been known to amount to a pint a day in cases which had not been recognised to be amœbic and properly treated. In a Calcutta series of liver abscess in Europeans, 20 per cent. opened through the lungs, nearly invariably the right.

lung, but very extensive Calcutta experience shows that this is rarely, if ever, the case. What happens is that the capsule of the liver becomes fused with the diaphragm and the pus escapes into the surrounding tissues to such an extent that the primary liver abscess cavity may shrink to the size of the tip of a finger and escape observation, while a small opening leads into a large secondary abscess in the base of the lung, or between the liver and the diaphragm. Much more rarely a right lobe abscess may open into the hepatic flexure of the colon, the duodenum, the peritoneum, the pericardium, or inferior vena cava, or it may come to the surface through or below the ribs, but such complications are rare under modern treatment. Acute general peritonitis following the open operation caused death in no less than thirteen of eighty-one fatal cases in Calcutta, and hæmorrhage after operation in five more.

Old encysted liver abscesses are met with occasionally in persons dying of other diseases in the endemic areas of amœbic disease; they are free from both amœbæ and bacteria, and contain clear fluid with a little granular *débris* but no pus cells. This is nature's method of cure in cases in which the causative protozoal organism dies out after a dense fibrous wall has formed around the abscess, and its occurrence shows that this method of cure is quite likely to be obtained by the use of a drug like emetine, which can kill the *E. histolytica* in the tissues.

Symptoms and Physical Signs. The early stages are those of the presuppurative congestion already described, and it is often very difficult or impossible to decide on purely clinical grounds whether suppuration has already taken place or not, except in the now rare cases in which the patient first comes under observation with obvious physical signs of a large abscess coming to the surface. Leucocytosis was formerly thought to be an indication of abscess formation, but there are records of many cases in which leucocytosis has occurred with counts as high as 30,000, and yet the disease has cleared up rapidly under the specific treatment. In the great majority of cases it is only the failure of treatment to reduce both the temperature and the leucocytosis that can be relied on as an indication that abscess formation has already taken place, but it is necessary to insist once more that in acute amœbic hepatitis with great congestion of the liver exploratory puncture should never be performed without a preliminary course of emetine to remove the congestion and the danger of fatal internal hæmorrhage which may result from puncture of the liver when in that state. In very chronic cases, on the other hand, there is little danger from an exploratory operation, and it should be remembered that this insidious form of abscess may be present in the absence of fever. It is also in these cases that only relative leucocytosis may be found, that is, a total leucocyte count of under 10,000, but accompanied by such a degree of anæmia than the leucocytosis would be equivalent

Ludlow in the much better climate of Korea had previously had a death rate of only 11·1 per cent. in 117 open operations. In 1936 he reported 133 open operations with 10·5 per cent., and 107 aspirations with 2·8 per cent. mortality, and stated that aspiration is the method of choice. At the Mayo clinic 14 per cent. of 125 liver-abscess cases were found to be amœbic in origin. A great reduction in the case mortality followed the introduction of the emetine treatment, with two deaths among eighteen, one of whom was moribund on admission. In Ceylon 47 cases treated by emetine, together with aspiration in four, all recovered ; one operated on died. Cases opening through the lungs do very well under emetine alone, and do not require any operative procedures. The open operation, if avoidable, is as unjustified as the opening of a tubercular psoas abscess or other large collection of pus which has not been contaminated with septic organisms.

Treatment

By Aspiration and Emetine. Now that this is the method of choice, it may be described first ; exceptional cases necessitating other measures will be dealt with afterwards. Emetine on injection has a special action on the liver, for experimental injections into rabbits by Parmer, with analyses at different intervals, has shown that the liver contains from five to twenty-four times as much of the drug as in the intestine, with the maximum after twelve hours, and thirteen times as much after four days. When a patient suffering from amœbic hepatitis has come under skilled treatment too late to avert suppuration, and suitable doses of emetine given for a week have failed to remove the fever, pain, enlargement of the liver and accompanying leucocytosis, it becomes advisable to perform the simple operation of aspiration to remove the accumulated pus. This procedure is not, however, absolutely essential in order to relieve his condition, for there are now numerous cases on record of large bulging, and even fluctuating, liver abscesses which have cleared up, apparently completely, under emetine alone, either in patients who have refused to be aspirated or in those in which the medical attendant has deliberately adopted the non-operative plan of treatment. The question is therefore one of expediency, for there is clear post-mortem evidence in patients dying later of some intercurrent disease that encystment of a liver abscess has been brought about by the drug alone, and in comparatively small abscesses encystment probably occurs frequently in cases which are regarded clinically as having been cured in the pre-suppurative stage.

The question, therefore, is whether the patient will recover more quickly under emetine alone or under the combined use of emetine and aspiration ? The evidence points to the latter procedure being preferable whenever the collection of pus is large enough to be found readily and removed by aspiration ; for it must be remembered that there is rarely less than ½ pint of pus in the cavity, and there may be as much

The case mortality of this class of case used to be 46 per cent., but it is almost *nil* under emetine treatment. Leucocytosis, with well under 90 per cent. of polymorphonuclears, helps to differentiate amœbic abscess of the lung from right basal lobar pneumonia, in which the polymorphonuclears usually form over 90 per cent. of the white cells.

Abscess of the spleen is a very rare complication of amœbiasis. It is usually sterile as regards bacteria and requires the same treatment as for amœbic liver abscess.

Amœbic abscess of the brain is another equally rare complication. Early recognition and active emetine treatment affords the best chance of recovery.

Prognosis

Under the obsolete *open operation in damp tropical countries* the mortality rate in 2,261 cases in the British Army in India was 56·7 per cent., in spite of the patients' being under skilled treatment from the beginning, and in 231 Calcutta cases it was 60 per cent. In 176 cases analysed by L. Rogers it was 73 per cent. in those opened through the ribs ; 59 in large right lobe abscesses opened below the right costal margin, but only 12 per cent. in small epigastric left lobe cases. This high mortality was due mainly to the secondary septic infection, which is almost inevitable in large amœbic liver abscesses opened in hot moist climates owing to air being sucked in and out of the wound at every breath during the frequent dressings required. After describing this condition, G. C. Spencer, when Professor of Surgery at the Royal Army Medical College, went on to say : "The great majority of amœbic abscesses are sterile when first opened, and every surgeon in India is familiar with the usual course of fatal cases—the patient does well for the first few days after operation, then infection occurs, the temperature goes up again, and death from septic poisoning slowly but surely follows." Moreover, E. O. Thurston, with a personal experience of 164 cases, concluded that "the open operation is to all intents and purposes obsolete except under unusual conditions."

On the other hand, by the method introduced by L. Rogers of one or more aspirations of the sterile pus, together with large doses of ipecacuanha orally, or, better, the daily injection of 1 grain of emetine, a very remarkable reduction of the mortality has been obtained. Thus, in 111 cases collected by the writer in Bengal the mortality was only 14·4 per cent., or one-fourth of the former rate, and that, too, in spite of the inclusion of many very bad cases which would have been considered almost hopeless in the days of the open operation, for several of the abscesses contained 6 pints of pus. Later still, K. K. Chatterji, of Calcutta, recorded 136 cases treated by this plan with a mortality rate of only 1·6 per cent., and A. L. Ludlow, in Korea, 50 cases with 2 per cent. of deaths, or only about one-thirtieth of that of the old open operation in the tropics, although it should be stated that

a dense fibrous wall nearly ½ inch thick, so this case illustrates how curative encystment is brought about. E. O. Thurston found that a single aspiration sufficed in 26 cases, two in 16 cases, three in 10 cases, and 4, 7 and 8 respectively in the remaining 3, although in two of the patients who recovered total amounts of 182 and 211 oz. were removed.

Cultures should be made from the pus which is first aspirated, and if numerous colonies of septic organisms grow on the plate, or if cocci can be found microscopically, secondary sepsis will be known to have developed already, so the cavity must be opened and drained. The appearance of a very few colonies in the culture tubes may be due to accidental contamination, and so does not necessarily indicate the need of drainage ; a number of such cases seen in Calcutta by the writer cleared up quite normally with aspiration and emetine. A. G. Biggam and P. Ghaldoungue (1933) have reported similar good results from aspiration and emetine in spite of the aspirated pus containing a few pus cells and bacteria, but if these are very numerous drainage is indicated. That septic infections are very rare is shown by a statement of R. S. Townsend that he could find no record of such an occurrence in an unopened liver abscess in a study of the British Army records in India. As sepsis and small non-adherent left lobe abscesses are almost the only indications for more serious surgical interference than aspiration, it is clear that very little scope remains for the obsolete open operation for amœbic liver abscess. A case of secondary infection of an amœbic liver abscess by *Ps. pyocyaneus*, found at the second aspiration, was treated successfully by sulphonamide drugs orally and the injection of 5 c.c. soluseptasine into the abscess cavity ; the dangerous open operation was thus avoided. Penicillin has been used for the same purpose with success.

In very rare cases of liver abscess, due to a strain of *E. histolytica* resistant to emetine, after repeated aspirations have failed, aseptic drainage may be necessary ; in such T. P. Kilner has used irrigation of the abscess cavity through a Carrel tube with Dakin's solution or eusol with success.

In a case of liver abscess rupturing into the abdominal cavity, with too severe collapse to admit of abdominal section, A. G. Biggam treated the patient successfully by aspirating the sterile chocolate-coloured pus from the abdomen.

Primary suture of liver abscesses after opening and swabbing out the cavity has also been used with great reduction in the period of convalescence, so this plan may be of use in small left lobe abscesses unsuitable for aspiration.

Specific Drug Treatment. The power of emetine to cause large amœbic liver abscesses to encyst is sufficiently striking, but even more conclusive evidence of its specific action is available in a case recorded by L. Rogers in which the liver of a patient, who had recently suffered from amœbic dysentery, was found at an exploratory laparotomy to

as 6 pints, the absorption of which must put a considerable strain on the patient's constitution and delay his recovery. Nevertheless, the absorption of several pints of pus under emetine treatment affords remarkable testimony to its specific action, and also indicates that the dangerous open operation is no longer justified except in the rare cases in which there is some strong surgical contra-indication to the emetine-aspiration method.

In very advanced cases still seen among indigenous patients in which a large liver abscess is clearly localised by pain, œdema and bulging the operation can often be done without a general anæsthetic. This procedure is advocated by K. K. Chatterji with a view to avoiding the deleterious effects of chloroform, which is especially dangerous when the liver is damaged. More frequently at the present time the disease is seen at an early stage and the site of the abscess is doubtful, so that several punctures may be necessary before the cavity is struck; in this case an anæsthetic will be required, but chloroform should be avoided if possible. A good-sized canula is advisable, as the pus may be thick. After removing as much as possible by aspiration, some advise that a large syringe be attached to the canula by a piece of thick pressure tubing and strong suction applied to remove as much as possible of the very thick remaining contents of the abscess. No drug need be injected into the cavity, as E. O. Thurston found that cases did just as well without quinine injections as with them. The essential point is to give emetine, and his plan of injecting 1 grain of emetine intramuscularly just after the aspiration, so that the drug may be carried through the wall of the abscess during the effusion of serum into its cavity after removal of the pus, is a good one, for it is thus most likely to reach the amœbæ in the active seat of the disease. As pointed out by J. C. Cantlie, the needle should not be thrust in for more than 3½ inches for fear of wounding a large vessel.

Anything up to six punctures in different parts of the hepatic region may be required; the epigastric region should be avoided unless the left lobe of the liver is considerably enlarged and adherent to the abdominal wall. It is in the small left lobe abscess that puncture may be most dangerous, and for this reason some surgeons prefer to make an incision under strict asepsis. In these cases the abscess is usually small, and so the risk of post-operative sepsis is much less.

Aspiration may have to be repeated after a week or so if the leucocytosis or fever persist and the cavity fills up again. As a rule the pus found at the second aspiration is considerably less, as in a patient from whom 86 oz. were removed at the first puncture, 16 oz. nine days later, 10 oz. at the third aspiration after another week, and after a further seven days only 5 oz. of thin fluid free from amœbæ or pus cells could be drawn off. The patient died a few days later of unconnected left apical lobar pneumonia, only 2½ oz. of encysted sterile thin fluid was found at the autopsy, and the

CHAPTER XIII

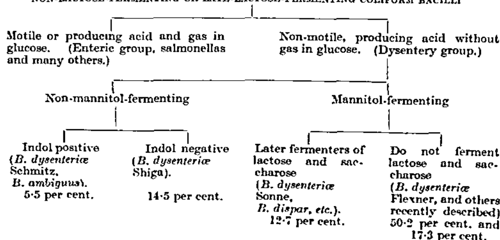
BACILLARY DYSENTERY

Definition. An acute inflammation or catarrh of the mucous membrane of the large intestine caused by bacilli of the dysentery group ; it is usually accompanied by fever, toxæmia, and the passage of frequent stools with blood and mucus. All cases of diarrhœa or dysentery which are caused by one of the dysentery bacilli are included under the term bacillary dysentery.

Historical. In 1898, Shiga isolated a bacillus of the typho-coli group from the stools of cases of acute dysentery in Japan, and showed that it was agglutinated by the serum of convalescent patients.

In 1900 Kruse found a similar organism in Europe, and Flexner isolated another type of bacillus which differed from the first-mentioned in that it fermented mannite. Subsequently a number of varieties of the Flexner type were separated by their serological reactions and absorption tests, which proved more reliable for this purpose than the unstable sugar tests advised by some workers. Further, the injection of the dead Shiga bacilli or their toxins into rabbits produces a specific necrotic inflammation of the mucous membrane of the large bowel similar to that of bacillary dysentery, and sera effective in treatment have been made by the aid of these toxins, so that the pathogenic properties of the bacilli are clearly established. Dysentery has also been produced on several occasions through the accidental swallowing of the Shiga organism, but the bacilli of the Flexner group, though clearly associated with the disease, do not comply with all Koch's postulates.

Classification of Dysentery Bacilli (Boyd)



(Based on an analysis of 7,339 strains of dysentery bacilli isolated in India.)

be riddled with very numerous small amœbic abscesses up to the size of a walnut ; yet the patient made a complete and lasting recovery under emetine injections. The use of emetine in the suppurative stage of amœbic hepatitis is similar to that already described under the earlier stage of the disease, so there is little to add. It is often advisable to give smaller doses, such as 0·5–0·75 grain morning and evening, rather than doses of 1–1½ grains once in twenty-four hours, especially in the case of persons of low body-weight. The injections may have to be continued for ten days or more, but it is rarely advisable to give more than a total of 12–14 grains in one course, except in very urgent cases, for fear of toxic effects which may result from its cumulative action. In patients who weigh less than 8 stone, the course should not exceed 8–9 grains, but after ten to fourteen days' interval a further shorter course may be given. The first result of the drug is the relief of pain, which may subside in one or two days after having been present for weeks. The temperature commonly falls to normal in three to seven days, and by the end of that time a definite decrease of the leucocytes may be found, although a longer time is required for the return of the count to normal. There is also usually a great improvement in the general condition of the patient.

It should always be remembered that emetine injections only act on the *E. histolytica* which are present in the tissues reached by the circulation, so after such a course it is advisable to give either emetine bismuth iodide or doses of 20–30 grains of ipecacuanha with 10 grains of tannic acid in mucilage and water last thing at night, three hours after a light meal, for a week, to clear up any infection in the bowel and so prevent relapse.

Chloroquine has been found to have an amœbacidal action *in vitro* greater than that of carbarsone, but less than that of emetine. It has been used successfully in the treatment of amœbic hepatitis, but is less effective on intestinal infections. Relapses may occur but yield to repetition of the drug. It is likely to be of special value in the rare infections that are resistant to emetine injections. The initial dose should be 1·0 gm. of the diphosphate followed by 0·5 gm. daily for two or three weeks.

LEONARD ROGERS

aerated media; this produces hæmorrhages and necrosis of the central nervous system of rabbits; and (2) an *endotoxin* set free by the disintegration of the bacilli, which produces the characteristic necrotic condition of the mucous membrane and is developed under anaerobic conditions. Dopter recognises only the endotoxins. Antitoxins are obtained by injections of the toxins into horses, in increasing doses, just as is done in the case of diphtheria. Anatoxins can be made by the action of formalin on the dysentery bacilli; they are of value in immunizing against the disease while being much less toxic than the dead bacilli themselves. On the other hand, bilivaccines orally have been tried extensively with adequate controls by army medical officers in India and found of no value as a prophylactic.

Dysentery bacilli are easily killed by heat or by drying, but their vitality is preserved by low temperatures, especially at the freezing point. They die out of stools in two days owing to the presence of other organisms, but may survive in damp soil for 100 days, in milk for 17 days, if no acid-forming bacilli are present, and in water for several days.

Persons convalescent from bacillary dysentery sometimes continue for long periods to pass the causative organisms from time to time in their stools, and may thus be sources of infection to others. They are known as carriers, and their presence accounts for the frequency of the disease in crowded institutions such as jails in the tropics and lunatic asylums in Europe. The insanitary habits of the inmates of lunatic asylums favour the spread of infection. In military camps and under war conditions bacillary dysentery is the prevailing form, and may become epidemic, as in the well-known case of the ill-fated Walcheren expedition long ago. In the Army in India bacillary dysentery is now the more prevalent type. As in the case of typhoid carriers cooks and others handling food may be dangerous, but in India Boyd doubted whether this mode of infection is common. This subject has been closely studied by J. Cunningham in Indian jails, and he has shown that carriers are nearly always really cases of latent dysentery in persons who have a mild chronic form of the disease. These cases can be detected if naked-eye examinations of the stools are made daily for ten to twelve consecutive days, as during that time the presence of mucus will almost certainly be detected. After isolating such persons from the rest of the prisoners no less than 97 per cent. of all the cases of dysentery in the jail occurred as relapses among the small number of latent carriers; infection of the remaining healthy persons was prevented by this simple plan of routine stool inspection and segregation which does not even require a laboratory. In English lunatic asylums the agglutination test, followed by bacteriological tests, has been used to detect and isolate carriers, with the result that dysentery has been almost eliminated from institutions in which it had long been a bugbear.

Table

Boyd's Classification of Mannitol Fermenting Dysentery Bacilli

New Name	Old Name
B. dysenteriæ Flexner I	Andrewes and Inman V
,, ,, II	,, ,, W
,, ,, III	,, ,, Z
,, ,, IV	Type 103
,, ,, V	,, P119
,, ,, VI	88-Newcastle-Manchester group
B. dysenteriæ Boyd I	Type 170
,, ,, II	,, P288
,, ,, III	,, DI

Ætiology. The Shiga bacillus causes a severe toxic type of dysentery with a considerable mortality, but the disease produced by the Flexner group of organisms is usually of a milder and less dangerous type. The bacilli gain access to the system through water and food, the latter being *often infected through the agency of flies*, and multiply in the large intestine, where they produce their pathological effects. In the early acute stage the bacilli can readily be isolated from the mucus in the stools or obtained by means of rectal swabs. R. Cruickshank reported nearly 100 per cent. positive results in this stage by means of cultures on desoxycholate-citrate agar and also a high proportion of successes during the second to the fourth weeks of convalescence and in the case of the not infrequent carriers among recovered patients. In chronic cases of the disease the causative bacilli are commonly absent from the stools in spite of the persistence of ulceration. Early bacteriological examinations should therefore be made when laboratory assistance is available. The medical practitioner ought to know how to select and send the most suitable material for the purpose. *Stools containing no mucus rarely yield positive results* on culture except in infections due to the Sonne type of bacillus ; when possible pieces of pure mucus passed as early as possible in the attack should be selected, and if the laboratory is not close at hand, an equal quantity of 3 per cent. sodium hydrate should be added, and the specimen kept as cool as possible. Even then the specimen will generally be useless unless it reaches the laboratory within six hours of being passed. Still better results will be obtained by examining mucus *freshly removed from the necrosed or ulcerated mucous membrane* through a proctoscope or sigmoidoscope tube, for in bacillary dysentery the lower portion of the large bowel is nearly always involved in the pathological process. Very exceptionally the dysentery *bacilli are to* be found in blood cultures.

The dysentery bacilli produce their necrotic effects on the intestinal mucous membrane through the toxins which they secrete, as is shown by the effect on rabbits of the injection of the dead bacilli or their toxins. Some authorities, especially P. K. Olitsky, maintain that the Shiga bacillus forms two toxins : (1) a soluble *exotoxin* in fluid well-

even in health, so that a single test is by no means conclusive evidence of the presence of active infection ; a steady rise in the titre is almost diagnostic. Wong has reported finding dysentery agglutinins in the colostrum and milk in over 80 per cent. of Chinese women admitted to lying-in wards, in some of whom dysentery bacilli were found in their stools.

Pathology. Both the naked-eye and microscopical changes in the bowel are quite distinctive in bacillary dysentery, in which the mucous membrane is the principal seat of the lesions ; whereas in amœbic dysentery the sub-mucous coat is primarily and mainly affected. The typical changes are best seen in the earlier stages of the disease, and they are naturally less distinctive in chronic cases when much scar tissue is formed. The process is essentially an inflammation of the mucous lining of the large bowel ; it may extend into the lower end of the ileum for a distance of one to three feet if the upper portion of the large intestine is involved and in this respect it differs from amœbic ulceration, which is nearly always strictly limited to the large bowel. The mucous membrane generally becomes thickened and infiltrated with a mass of small round cells, and on its surface a fibrinous deposit is found, usually of a greenish colour and thickest on the summits of the transverse folds of the mucous membrane or rugæ, where it presents a characteristic granular appearance. In other parts ulceration may have taken place owing to sloughing away of portions of the inflamed mucous membrane. The result is the formation of slightly depressed transverse or irregular serpiginous ulcers, which run into each other, on the surface of the generally thickened mucous membrane. These ulcers present just the opposite appearance to the raised rounded or oval amœbic ulcers between which there is healthy mucous membrane. In acute cases of bacillary dysentery after death the whole length of the large bowel, together with the lowest part of the ileum, are found to be continuously affected, but in chronic cases, terminating more than a month after the onset, only the lower half or two-thirds of the large bowel is involved as a rule, although a few scars of old ulcers may be observed higher up. Apparently the more generalised condition is accompanied by so much toxæmia that death takes place within the first few weeks after its onset, and longer survival only occurs with less extensive disease. In very acute rapidly fatal cases the bowel wall may be so acutely inflamed that it may measure half an inch in thickness and be covered with a dense white fibrinous membrane, constituting the diphtheritic dysentery of older writers. In such cases the patient may die of overwhelming toxæmia before ulceration has had time to occur.

In chronic bacillary dysentery the lower half or so of the large bowel is generally thickened and very extensively ulcerated, so that in considerable areas only small tags of mucous membrane remain between nearly continuous ulceration of a very irregular character ;

Flies play an important part in the dissemination of dysentery owing to their habit of feeding on fæcal matter and subsequently contaminating any human food on which they happen to pass their fæces, which have been proved to contain dysentery bacilli during epidemics. Fly dissemination is in accordance with the seasonal distribution of the disease in India and other tropical areas, for the cases increase during the early hot-weather months when the flies are multiplying, it decreases to some extent in the hottest months when the flies are fewer, and rises again to its maximum in the warm rainy season and autumn months, when flies once more abound. J. C. G. Ledingham found a similar relationship in Mesopotamia with two epidemic rises which followed the spring and autumn fly seasons, while there were fewer cases in the hot dry season when the flies were diminished in numbers. During this slack season human carriers kept up a moderate amount of the disease. Efficient trenching of night soil and protection of food from flies are therefore very important prophylactic measures against dysentery. In the North African campaigns of 1940–43 fly-proof latrines with automatically closing lids proved to be of value. The occurrence of the disease in dogs has also been recorded by Dodd in China and is regarded by him as a possible source of infection.

The Agglutination Test is of considerable value in the diagnosis of chronic bacillary dysentery cases and in the detection of carriers, but owing to the fact that it does not become positive until about the tenth to the fourteenth day in 50 per cent. of the cases, and even in the third and fourth week it is positive in only 82 per cent., it is useless in the early diagnosis. The reaction is often lost rather rapidly in convalescent patients, so that negative reactions are of little value in retrospective diagnosis. In one series only 87 per cent. still gave reactions six months after recovery. Owing to the existence of a number of types of dysentery bacilli the test should be made against the Shiga organism and against a mixture of the various types of Flexner bacilli, and as the latter may vary in different countries those which are specially prevalent in the locality should be utilised. For the selection of suitable strains of bacilli for the tests J. S. K. Boyd uses Shiga and Schmitz anti-sera for the non-mannitol fermenting group ; for the mannitol fermenting forms he uses an anti-Sonne serum, a polyvalent one for the Andrewes' races and a third for the remaining varieties. For typing the different races he advises a series of non-specific serums, obtained by absorbing out the group agglutinin. With these clear results can be obtained in a few minutes with a slide-agglutination test. The macroscopical test is the more reliable, and with the Shiga bacillus agglutination in dilutions of 1 in 25 to 1 in 50 is diagnostic, but with the Flexner group nothing less than 1 in 50 to 1 in 100 should be relied on. It must also be remembered that an appreciable percentage of the population in many tropical countries give positive reactions

Microscopically, the following cellular elements are found in smears : (1) large macrophage cells or corpuscles without definite structure ; these are very likely to be mistaken by the inexperienced for dead amœbæ which have lost their motility ; they may be numerous and

BACILLARY DYSENTERY

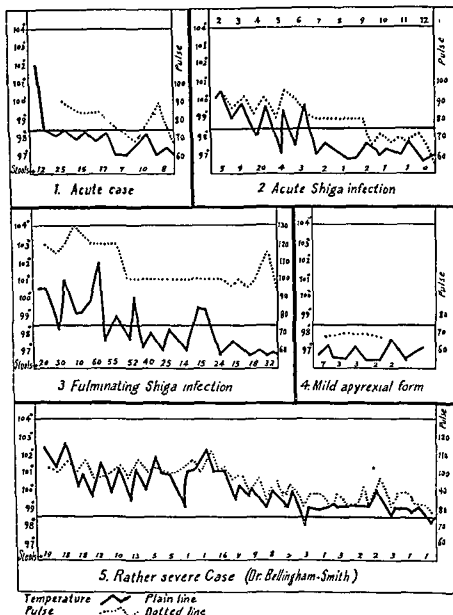


FIG. 44. Temperature and pulse charts.

are characteristic of bacillary dysentery ; (2) numerous desquamated columnar epithelial cells are seen in many cases ; and (3) the most constant feature is the presence of very large numbers of leucocytes, some 90 per cent. of which will be polymorphonuclears. These usually stain well in early acute cases, and they cause the exudate to differ

the ulcerated portions are depressed, and the remaining portions of mucous membrane are raised between them. The sigmoid and rectum are nearly always involved, so that the diseased condition can be seen with the proctoscope or sigmoidoscope ; the floors of the ulcers have a red congested appearance, and do not show the tawny yellow infiltration of amœbic disease. The bowel is also much more sensitive to touch, and the passage of the instruments is attended with more pain than in amœbic ulceration. The extensive destruction of the mucous membrane in these chronic cases makes healing a slow and difficult process, especially as there is no specific treatment for this stage of the disease. The practitioner who has opportunities of seeing the end results of bacillary dysentery at autopsies will be able to learn valuable lessons as a guide to rational and patient treatment, and he will also realise the absolute importance of recognising the nature of the disease and treating it efficiently at the earliest possible moment in order to avert serious and too often irreparable destruction of the mucous membrane of the bowel.

The microscopical changes can be described briefly. In the early stages they consist of a copious small-celled infiltration of the mucous membrane which is so intense as to hide the tube glands, and later of necrosis and desquamation of the mucosa. Both processes are found in different areas of the bowel at the same time. The submucous coat is much congested, but as a rule only slightly thickened, except in extremely acute cases, with much œdema of the bowel wall, while the muscular and peritoneal coats are little if at all affected. In the more chronic cases the mucous membrane is largely replaced by granulation tissue with considerable formation of fibrous tissue in floors of the ulcers, whose edges slope down to the floor from the surrounding portions of the mucous membrane. The mucosa does not overhang the edges of the ulcers in the way that is so common in amœbic disease, in which the infiltration of the submucous coat leads to undermining of the surrounding healthy mucous membrane. In the bacillary disease the mucous membrane between the ulcers becomes inflamed or necrosed.

The naked-eye and microscopical characters of the stools are of considerable diagnostic importance. The mucus passed in early acute cases consists chiefly of pieces of fibrinous deposit from the surface of the inflamed mucous membrane ; these fragments contain large numbers of polynuclear leucocytes and may also show small masses of columnar epithelial cells. The bowel discharge may also consist of white gelatinous mucus ; this adheres to the vessel, which can be turned upside down without the contents falling out. The presence of this tenacious mucus is a sign of a very acute condition. More frequently blood-stained rosy mucus is seen which cannot be distinguished by the naked eye from that of other forms of dysentery, and it is in such cases that the microscope is of such value in making a diagnosis.

palpation over the sigmoid and descending colon, and in severe cases it may also be noted over other parts of the colon up as far as the right iliac fossa, although the cæcum is much less often involved than in amœbic disease.

The number and character of the stools vary enormously in different cases from almost continuous passage of motions down to five or six daily. The frequency of the stools is of little or no value in differentiating between the different forms of dysentery. The bacillary cases due to the Shiga bacillus are much more severe on the average than those of the Flexner type, especially as regards fever and toxæmia. The naked-eye and microscopical characters of the evacuations have already been described, and the value of the microscope in the differential diagnosis has been emphasised.

The blood changes are not very characteristic ; leucocytosis, either actual or relative, is rather unusual in comparison with its frequency in amœbic dysentery. Any considerable increase in the leucocytes is only met with in acute cases, and even in these the total number rarely exceeds 15,000, so that the occurrence of high counts in acute cases and of any increase, either actual or relative to the red corpuscles, is in favour of the presence of the amœbic as against the bacillary type of dysentery. In chronic uncomplicated bacillary dysentery leucocytosis is very rarely met with, although it is common in amœbic disease if relative leucocytosis is included. The red corpuscles may show high counts in the acute choleraic form owing to the loss of fluid from the system ; when this occurs it constitutes an indication for saline injections. In chronic cases some degree of anæmia may be present, but it is not so common as in amœbiasis of the bowel. Observers in Peking report that the pernicious type is most common and that it responds to liver treatment. The chlorides in the blood are also reduced.

The course of an average acute primary bacillary infection depends mainly on the efficiency or otherwise of the treatment adopted, and especially on the stage already reached when the patient comes under observation ; everything depends on the use of proper measures at the earliest possible moment after the onset of the attack, just as is the case with cholera. We have only to recall to mind the acutely inflamed and congested state of a large area of the mucous membrane of the large bowel to realise the urgent necessity of relieving that condition before the onset of extensive necrosis, which may be followed by intractable ulceration. The damage may be done within a few hours, and the loss of a day will nearly always greatly prolong the course of the disease and lead to a slow convalescence. The necessity for losing no time in calling in medical aid immediately on the occurrence of the very first sign of dysentery should be impressed on all persons going to the tropics, for at this stage relief can generally be afforded within twenty-four hours, and what would otherwise become a serious illness

materially from that of amœbic disease, in which there are few cells and a very small percentage of polymorphonuclears, but a high proportion of degenerated mononuclear cells. Red corpuscles may be present, but they are scattered and not found in the clumps so common in the amœbic disease.

Clinical Description

Acute Primary Attacks. First attacks of bacillary dysentery are usually acute and definite, although they may vary in intensity from very dangerous cholera-like cases through typical acute dysenteric attacks down to the mildest forms in which there is only diarrhœa with small flakes of mucus in the stools. The main characteristics of typical cases are an acute onset accompanied by a considerable degree of fever, numerous stools containing blood and mucus with or without the addition of fæcal matter ; there is a good deal of abdominal pain and straining due to involvement of the rectum and sigmoid ; toxæmia and prostration of variable degree is usually present. (*See* Fig. 44 for Temperature Charts.)

The temperature curve is commonly of a remittent type at first, becoming intermittent after a few days, and, in severe cases, it may even resemble that of a typhoid fever ; cases of dysentery have sometimes been mistaken for typhoid, and this is not surprising considering the close relationship of the causative organisms of the two diseases. It is common for two or more cases to occur at the same time in a household ; when this happens, especially if the patients are children, the disease is likely to be of the bacillary rather than the amœbic type. Bacillary dysentery is the form which occurs in epidemics, especially the severe form due to the Shiga bacillus. Under efficient treatment the temperature usually declines gradually to normal in a week or two, but as long as it continues to rise, even to just over 99° F., active symptoms are likely to persist, and continued care is necessary to avoid a recrudescence of acute symptoms. A decline for several days to a slightly subnormal level, such as 97° to 98° F., is a favourable sign.

Abdominal symptoms appear very early, beginning with discomfort, going on quickly to griping pain and the passage of blood and mucus with straining, and followed by tenesmus. These symptoms result from the irritation of the lowest part of the large bowel, which causes a feeling of bearing down and continuous desire to go to stool, although only a little mucus may be passed each time. A dull pain is frequently referred to the neighbourhood of the navel or across the lower abdomen. Localised pain and tenderness are not so frequent in bacillary as in amœbic dysentery ; in the latter disease the bowel lesions are more localised, and more frequently the inflammation extends through to the peritoneal coat of the bowel. Some thickening or contraction of the large bowel is generally to be detected in bacillary dysentery on

relapses. Nevertheless, it is only by microscopical examinations of the stools that the chronic cases of the two main types of dysentery can be differentiated. It should be remembered that it is very difficult to isolate the dysentery bacilli in the chronic stage when there is secondary infection of the bowel ulcers, and failure to detect the bacillus does not justify the exclusion of bacillary dysentery ; J. Cunningham, in Indian jails, obtained positive bacteriological results in only 26·7 per cent. of chronic cases, and then most frequently during an acute exacerbation of the affection.

In these emaciated patients the abdomen is retracted, but by palpation thickening of the descending colon and sigmoid can often be detected. As a rule there are no local signs in the right iliac fossa. because only the lower half or two-thirds of the large bowel is ulcerated in chronic bacillary disease ; this is an important point of differentiation from chronic or latent amœbic disease, in which there is localisation of the ulcers in the upper end of the large bowel. The stools are often foul-smelling in bad cases in this stage, but the odour is different from that of stools in the amœbic disease. It must be borne in mind that in a small percentage of cases both amœbic and bacillary dysentery may be present at one time ; when this occurs the treatment has to be modified to suit the condition. Moreover, bacillary dysentery often occurs as a terminal infection in patients debilitated by such chronic diseases as neglected malaria and kala-azar.

Complications. The inflammatory process in bacillary dysentery is essentially confined to the mucous membrane, so that localised peritonitis is rare over the sites of the lesions, as is perforation, whereas they are much more common in amœbic infections. Stenosis of the large bowel is a very rare complication in chronic cases. The most important complication of bacillary dysentery is a toxic *arthritis* of large joints, especially the knees, ankles, elbows, fingers, shoulders and wrists, in that order of frequency according to Z. Cope. Arthritis occurs most frequently in Shiga infections and usually comes on within the first three or four weeks of the disease, but it may appear any time up to three months. The attack begins with fever and pain in one or more joints, followed by the effusion of sterile fluid ; this may clear up in a few days or take months for complete recovery ; it is rarely followed by stiffness or ankylosis, and no treatment appears to affect its course. In very rare cases the Shiga bacillus has been isolated from the fluid removed from infected joints. Myocarditis, pericarditis and in one instance abscess of the spleen containing Flexner's bacillus have been seen post-mortem.

Conjunctivitis and **iritis** are also met with ; the former often accompanies arthritis, but they usually clear up without leaving any after-effects and are also toxic in origin. Urethritis, parotitis and polyneuritis are rare sequelæ of the disease.

The liver is very rarely affected in bacillary dysentery, which never

may be reduced to a mild affection of short duration. In patients who are not fortunate enough to come under skilled treatment on the first day of the disease the symptoms are likely to increase in severity; pain and tenesmus will become more constant with the passage of very frequent stools, often of pure blood and mucus; the temperature will remain high, and toxic symptoms with great prostration will ensue, resembling the typhoid state. If the patient survives the acute stage extensive ulceration of the large bowel will remain and will require prolonged medical care for its successful treatment. Too often there will remain permanent deterioration of health, which may necessitate the abandonment of a promising career in a tropical country. In the milder cases a good recovery is likely to take place even in the absence of treatment.

In very acute choleraic or fulminant bacillary dysentery there may be great loss of fluid by the bowel at first. This may even lead to a mistaken diagnosis of cholera, but no harm will result if the mistake leads to the employment of the saline treatment, which will be indicated by finding a high specific gravity of the blood, such as 1062 to 1064 in place of the normal reading of about 1056 to 1058. In these cases there will be a high temperature if the patient is not collapsed from loss of fluid and toxæmia, and such patients are not infrequently pulseless as in cholera itself; death will soon ensue unless immediate treatment on the lines described under cholera is carried out. With suitable treatment many cases can be restored from a nearly moribund condition. These toxic cases nearly always prove to be due to the Shiga bacillus.

Chronic bacillary dysentery is usually due to the neglect of efficient treatment in the early stages of the acute disease, and the intractable and miserable condition of this class of patients serves to emphasise still more strongly the importance of proper treatment at the outset. The febrile stage is now past, apart from occasional rises of temperature to 99° or 100° F., with exacerbations of the bowel symptoms. The patient will be greatly emaciated, and in bad cases anæmia and œdema of the lower extremities will be present, producing a pitiable condition. Several loose stools will be passed daily, and they now usually consist of fæcal matter containing small flakes of mucus, best seen by washing the stools as described under the amœbic disease (p. 227). The daily progress of the case can best be followed by systematic washing of the stools and observation of the amount of mucous discharge, which will be greater the larger the unhealed ulcerated surfaces in the bowel and the more active the dysenteric process. This stage is met with in patients who have suffered from dysentery for periods varying from one month to several years, and as a rule the patient has never been entirely free from bowel trouble for any great length of time since the first attack. In this respect the bacillary disease differs from the amœbic, in which considerable intervals of health occur between the

relapses. Nevertheless, it is only by microscopical examinations of the stools that the chronic cases of the two main types of dysentery can be differentiated. It should be remembered that it is very difficult to isolate the dysentery bacilli in the chronic stage when there is secondary infection of the bowel ulcers, and failure to detect the bacillus does not justify the exclusion of bacillary dysentery ; J. Cunningham, in Indian jails, obtained positive bacteriological results in only 26·7 per cent. of chronic cases, and then most frequently during an acute exacerbation of the affection.

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as the urgent need of immediate correct treatment is no longer present, and if daily 1-grain injections of emetine fail to ameliorate the condition greatly within a few days it is almost safe to exclude amœbic infection ; this greatly increases the probability that chronic bacillary dysentery is responsible for the symptoms. It is necessary, however, to exclude the forms due to schistosomes and balantidium coli by microscopical examinations of the stools if the patient has lived in a country in which these parasites occur. A normal leucocyte count would be somewhat in favour of bacillary as against amœbic disease, while the presence of leucocytosis is much against the former.

Proctoscopic and Sigmoidoscopic Examinations. Important confirmation of the diagnosis and an opportunity of obtaining fresh material from any ulcers found for microscopical and bacteriological examinations may be obtained by examinations per rectum by these instruments. The sigmoidoscope allows of the inspection of a much greater length of the lower bowel, but it is a dangerous instrument in unskilled hands and its use is often attended by much pain in bacillary dysentery more particularly. On the other hand, the simpler proctoscope frequently suffices for diagnostic purposes. Proctoscopy in the knee-elbow position permits of early and accurate diagnosis in up to 90 per cent. of cases. The method is of most use and also less painful in chronic cases.

Prognosis and Mortality. The very acute epidemic cases of bacillary dysentery are always liable to be serious, and may have a high case mortality, but very early and correct treatment will save many patients who would be very difficult to deal with successfully if not seen in the first day or two. Continued high temperature, the passage of numerous stools of pure blood and mucus, or of watery stools simulating cholera, with prostration or collapse and persistent hiccough from severe toxæmia, are all indicative of a grave condition, although they may be overcome in some cases by hypertonic saline injections intravenously as in cholera.

Chronic cases if over one month in duration, especially in feeble persons belonging to tropical races, are particularly difficult to treat owing to the great extent of the ulceration of the colon. When the patient has already become emaciated and anæmic, and especially if œdema of the feet is present, the prognosis is grave.

The mortality varies exceedingly in the acute stage, from 30 per cent. in Japanese epidemics of the Shiga type, down to a very low percentage in mild cases. In the chronic stage in Indian patients, in Calcutta, the death rate is from 30 to 40 per cent., and among Mecca pilgrims it used to be up to 64 per cent. in dysentery cases before the use of the serum treatment, but was reduced by its use to 10·8 per cent. and Manson-Bahr also obtained a great reduction by the same method in Fiji. The earlier the case comes under treatment, the better the prognosis.

produces the form of hepatitis going on to large tropical abscess, which is peculiar to the amœbic disease. Nor was septic suppurative pylephlebitis ever met with by the writer in very numerous dysentery post-mortems in two decades in Calcutta ; multiple small liver abscesses always proved on microscopical examination to be purely amœbic in origin. This is rather surprising considering the extensive ulceration which occurs in many bacillary cases, but the freedom from secondary infection of the liver is probably due to the fact that the pathogenic process is practically limited to the mucous membrane, and a large amount of protective fibrous tissue formation occurs in chronic ulceration of this nature. Intussusception may be found in fatal cases, especially in children. In severe cases of bacillary dysentery, J. C. Dick noted signs of kidney lesions with albuminuria, casts and increased blood urea with glomerular congestion and catarrhal changes in the convoluted tubes in fatal cases. N. H. Fairley and J. S. K. Boyd noted similar conditions in cases not receiving sulphaguanidine treatment.

Diagnosis. In acute cases high temperature with signs of toxæmia and the passage of pure white glutinous mucus should cause bacillary dysentery to be suspected ; a microscopical examination of the mucus will reveal the presence of the typical cellular changes already described, and also the absence of *E. histolytica*, and thus lead to early correct diagnosis and treatment. If a bacteriological examination of the fresh stool is available the dysentery bacilli should be sought for to confirm the clinical diagnosis. The absence of leucocytosis is in favour of bacillary as against amœbic disease in an acute case, but the agglutination test is useless in the all-important early stages. The fulminant choleraic type can only be distinguished from cholera itself by the character of the stools and by the absence of the characteristic vibrios of cholera from the stools on microscopical examination. Fortunately, the most essential treatment of both conditions is the same, namely, the very early administration of hypertonic salines intravenously.

In chronic cases the clinical manifestations are even less distinctive, although the thickening of the bowel in the left iliac fossa is in favour of the bacillary, and in the right of amœbic disease. The naked-eye appearances of the stools now are much the same in both diseases, but the microscopical characters are of greater value, although not to the same extent as in the earlier stages, except when the *E. histolytica* is found, which will show amœbic disease to be present. The finding of the *E. histolytica* does not exclude the possibility of coincident bacillary disease, as both affections are occasionally present together. It is in these cases that a positive agglutination reaction with one of the strains of dysentery bacilli is of the greatest positive value in the recognition of bacillary dysentery of over ten to fourteen days' duration. If all these points fail the emetine test may be employed in chronic cases,

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Sulphonamides. Sulphaguanidine has been most used on account of its relatively insolubility, which allows of its more direct action on the large bowel, but it is rather costly on account of the large doses required. Healing of ulcers can be observed in chronic cases through the sigmoidoscope. In acute cases 20 gm. are given daily by the mouth up to a total of 140 gm. In mild ones 20 gm. on the first day and 10 gm. on three subsequent days may suffice, but extensive war experience indicated the continuance of 10 gm. doses for about fifteen days to prevent relapses and to eliminate carriers. Others consider sulphadiazine to be more effective, especially in early cases, and to be more rapid in both its clinical action and in causing the stools to become negative as regards dysentery bacilli. Succinylsulphathiazole is advocated by others.

Bacteriophage treatment has been tried by a number of workers during the last two decades and very variable results have been reported. The majority of the most reliable workers have observed no benefit from its use.

Hypertonic salines, given intravenously for preference, but also of use intramuscularly or subcutaneously, were first shown by L. Rogers to be of life-saving value in the acute choleraic and highly toxic bacillary dysentery, and this observation was confirmed during the war of 1914–18 by Graham and others. In addition to overcoming collapse the excess of chlorides combines with the toxins in the system and causes them to be excreted through the kidneys, as was pointed out by Benjamin Moore in the case of cholera toxins. Hypertonic salines are also indicated by the finding of G. Walther and L. Günther of hypochloræmia in Flexner dysentery cases. They gave 20–40 c.c. of a 10–20 per cent. solution intravenously with benefit. Serum can be combined with the saline as already mentioned.

The pain and straining are soon relieved by the production of free watery fæcal stools, but if the diarrhœa is so severe as to produce shock and prevent sleep, morphia may have to be given, either orally or subcutaneously; it is preferable to opium as being less constipating. Hot fomentations or hot-water bottles to the abdomen, or turpentine stupes, are also of value in relieving discomfort.

The diet is very important and only fluids should be given at first, preferably broths or Brand's essence, albumen-water, rice-water and jellies, but milk may do harm by producing curds in the acute stage.

Treatment

Early Acute Cases. Salines. The treatment of bacillary dysentery in the early acute stage is quite different from that which is suitable to chronic cases of the disease, and the former will be considered first. Bearing in mind the acutely congested state of the mucous membrane, caused by the irritant toxins, the first indication is to relieve it by saline purges, which drain away the inflammatory œdema, and at the same time relieve the pain and straining, and bring away fæcal matter which is retained when only blood and mucus are being passed. A nearly saturated solution, such as 2 drachms each of sodium sulphate and magnesium sulphate in 1 oz. of water, should be given. The initial dose is 1 oz., followed by 2 drachms, containing 1 drachm of the salts, every hour until free watery motions are passed, when the frequency may be reduced to every four hours. The solution is continued until all acute symptoms are relieved and blood and mucus cease to be passed. In mild cases this result may be attained in two or three days. There are few more satisfactory experiences in medicine than the rapid relief of the distress of an acute attack of dysentery which is afforded in early cases by this treatment, and, as a rule, nothing more is required in them. The loss of a day or two in starting the salts will, however, greatly prolong the convalescence of the patient by allowing time for the toxins to produce ulceration before the congestion of the large bowel is relieved. As a preliminary purge is also required in early amœbic disease, there need be no hesitation in giving salines, even if it has not been possible to make a microscopical examination of the stools. Another point is that the amœbæ are often more easily found after a purge than before.

Some prefer other purgatives, such as 2 oz. of castor oil on the first day and 1 drachm hourly during the daytime on the second and third days, or Turkey rhubarb in half-teaspoonful doses every two hours until the drug appears in the stools. For children 5-grain doses are suitable, and castor oil is also of value in the treatment of bacillary dysentery in childhood.

Anti-dysenteric Serum is of great value in severe toxic acute cases of bacillary dysentery, especially those due to the Shiga type of organism, in which 5,000 to 10,000 international units are usually recommended to be given either intramuscularly or intravenously, when it may be diluted with normal or hypertonic salines. It is important to commence its use as early as possible in severe Shiga infections and it should be repeated daily as long as toxic symptoms continue. It is obtainable of a strength of 10,000 I.U. in 1 c.c., and N. H. Fairley and J. S. K. Boyd advise 5 to 10 c.c. doses containing 100,000 to 200,000 I.U. intravenously daily as long as is necessary. It is complementary to the sulphaguanidine treatment as it neutralises the toxins which are not affected by the sulphonamide drugs. It is not required in non-toxic cases.

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The patient should be encouraged to take plenty of liquid in the form of frequent small sips ; a little orange juice should be added to some of the drinks. In the later stages arrowroot and sago may be added, and two-hourly small feeds are indicated, but these should be only slightly warmed. The diet must be increased with very great caution as the condition of the patient improves. Any undue haste to get on to solid food is liable to be followed by a relapse, and the slightest rise of temperature to over 99° F. should be regarded as a sign that the disease has not yet completely subsided, so that no increase of the diet should be attempted. During convalescence the diet, even while still liquid, should have a gradual increase in its protein content, and the need for all the essential vitamins must not be forgotten.

Treatment of Chronic Bacillary Dysentery

When the early acute stage is untreated, or incorrectly treated, extensive necrosis of the mucous membrane rapidly ensues and quick recovery is no longer possible. Many cases in the tropics among the indigenous races do not come under observation till after some weeks or months of dysenteric evacuations, and successful treatment at this stage is a matter of great difficulty. As the early congestive stage is now a thing of the past, salines are no longer effective and may tend further to exhaust the patient, but an occasional dose of castor oil may be used to clear the bowels of fæcal matter. In mild cases a course of milk diet with small doses of castor oil in the form of emulsion often has an excellent effect. Bismuth subnitrate in drachm doses may with advantage be added to each dose of the emulsion. Drugs given by the mouth have little effect, as by the time they reach the irritable ulcerated portion of the colon, which is nearly always the lower half, as mentioned under pathology, they are soon evacuated in the stools. For this reason, *medicated and cleansing enemata* acting directly on the ulcerated surfaces of the lower portions of the large bowel form an *important class of remedies in chronic bacillary dysentery*, and a variety have been recommended from time to time. They are run into the upper part of the rectum through a soft tube attached to a cylindrical graduated glass funnel raised only 1 to 2 feet above the level of the hips, so as to pass the fluid in slowly with the patient in the right lateral or genupectoral position. Half an ounce of castor oil should be given on the previous evening, and in the morning the bowel should be washed out with an alkaline enema of 60 grains of sodium bicarbonate to the pint shortly before the medicated enema is given.

The most effective preparations are silver and copper salts, especially the former. Silver nitrate has been most used in strengths varying from 1 in 500 to 1 in 100, or 1 to 5 grains per ounce of distilled or pure water, beginning with a weak solution on account of the pain which is sometimes produced, and working up to the stronger ones if well

borne. If pain persists after the injection, it can be stopped by a salt and water enema, which precipitates the silver salt, as does albumen. The writer found that in the presence of small quantities of sodium chloride and albumen silver nitrate was very much less effective in destroying dysentery bacilli *in vitro* than when it was dissolved in pure water, but that silver albuminate (albargin) and silver nucleate (nargol) were equally effective in either solution, and in the presence of broth they killed the dysentery bacilli in dilutions of 1 in 1,000 in a few minutes, while under these conditions silver nitrate only killed them in 1 in 100 dilutions. He therefore recommended 1 grain to the ounce of these silver preparations as a medicated enema in chronic bacillary dysentery, and found that they were often effective and were painless even in young children, but they are rather expensive. A complex colloidal combination of albumin with the diacetyl-tannic acid silver salt called targesin, also has a lethal action on dysentery bacilli *in vitro*. It has been recommended in doses of two tablets orally three times a day.

Copper sulphate in a strength of 1 grain to the ounce is often of value, and is less painful than silver nitrate. Sodium chloride solutions, including sea-water, and also eusol in the proportion of 5 oz. to a pint, have also been recommended. The latter may be painful, and would probably be more effective if given in weaker solutions. Weak permanganate solutions are also useful. Chiniofon (yatren) is also used in bacillary dysentery in a similar manner to that described under the amœbic disease (p. 236).

Vaccines are sometimes of considerable value in chronic bacillary dysentery. In the case of the Shiga bacillus the toxicity must be neutralised by treating the cultures with Shiga serum or formalin when preparing the vaccine, or a small dose of serum may be injected at the same time as the vaccine ; this is unnecessary in the case of the non-toxic Flexner types. Initial small doses of 10,000 to 100,000 may be gradually increased to several millions. Large doses given by the mouth are less effective, and variable results have been reported from the prophylactic use of the vaccines by either route. The best results are likely to be obtained with vaccines made from the local strains in cases in which dysentery bacilli are still demonstrable in the stools. More accurately controlled trials are required to establish the indications for this line of treatment.

Diet is a very important and difficult problem in chronic dysentery ; it is necessary to give adequate nourishment of a bland and unirritating nature, and to continue the special diet for long periods, as any attempt to hurry matters only too often produces a recurrence of bowel symptoms. Red meat must be avoided for a long time, and also cheese and other not easily digested foods and vegetables, but fruit is often beneficial. Orange juice can always be given with advantage when the patient is on an invalid diet. The patient will soon learn from

experience what suits him and what he must avoid, and he must then stick for months to a diet which excludes all things found to be unsuitable. Alcohol is injurious, and should be avoided. An adequate supply of the essential vitamins should be provided.

Cold should be avoided, and a flannel binder worn around the abdomen is useful to prevent chills. Bathing in cold water should be prohibited.

Surgical Treatment. In obstinate cases with very extensive and intractable ulceration of the colon all medicinal measures may fail to prevent the patient from gradually going down hill, and the only chance of saving his life may be the use of surgical measures to divert the fæcal matter from the large bowel, and so give the ulcers complete rest from irritation and afford them a chance of healing. This line of treatment is very disagreeable and prolonged, and the decision when to make use of it is a most difficult one, for every other method of treatment should be exhausted before it is resorted to ; yet to leave it too late until the patient has become extremely emaciated and weak will not give it a fair chance. Much experience is necessary in coming to a decision, as each case must be judged on its merits and no hard-and-fast rules can be laid down.

Appendicostomy was formerly used a good deal for irrigating through the large bowel in these cases, but has largely been abandoned as of little value, as it does not divert the fæcal stream from the ulcerated surfaces, and as these are nearly always situated in the lower half of the large bowel in chronic bacillary dysentery they can be reached satisfactorily by medicated enemata.

Ileostomy was used during the war of 1914–18 in some cases, but it has the disadvantage that subsequent closure of the wound is not easy. **Cæcostomy** is now more generally used in the fortunately rare cases in which drastic surgical interference is called for ; P. Manson-Bahr and A. L. Gregg advise a muscle splitting operation with excision of the appendix, the insertion of a Paul tube, and the early fitting of a colostomy belt. The drainage must be continued for months until some time after healing of the ulcers, as shown by the sigmoidoscope, and until all pain has ceased and the general health of the patient has improved. Trials may be made of allowing the fæcal matter to pass into the colon by applying a pad over the opening, and it is better to err on the safe side rather than to risk failure by premature closing of the opening. The mortality in these very serious cases is high, but a few may be saved by timely surgical intervention.

LEONARD ROGERS

CHAPTER XIV

CHOLERA

Definition. Cholera is an acute specific disease caused by the comma bacillus (*Vibrio choleræ*). It is conveyed by ingestion usually through infected food or water. The disease is characterised by very copious colourless watery stools producing collapse through loss of fluid from the blood, followed by suppression of urine. There is a high mortality unless efficient treatment is promptly carried out.

Historical. The disease was probably known to Susruta in India in the seventh century, and it has probably also been endemic in China for thousands of years.

In 1817 and 1818 cholera spread all over India from Bengal and the east of the United Provinces, where it was endemic in the autumn of 1817; it ceased to spread, as usual during the winter months, but in March, 1818, it spread rapidly from Bengal and the United Provinces to the Punjab, the Central Provinces, Bombay and the whole of the peninsula during the next nine months, and culminated in the worst epidemic known.

The first pandemic of the nineteenth century spread from north-east India in 1826 through the Punjab and Central Asia by the overland route through Afghanistan and Persia, to reach Europe through South Russia in 1830, and America in 1832; it thus took five years to travel from Bengal to Europe in the absence of rapid means of communication by rail and sea.

In 1840–49 another pandemic spread overland through Asia to Europe and on to America by sea; it is said to have carried off one million people in Europe, and it caused 53,293 deaths in England.

In 1848–53 a new pandemic spread by sea from Bombay to Basra in the Persian Gulf and on to Europe and America.

In 1863–66 the disease was carried by sea from Bombay to Egypt, and affected southern and western Europe and North America.

In 1866–70, and again in 1892–94, cholera spread from the Punjab in north-west India by the overland route to Russia. It is noteworthy that the latter epidemic originated at the Hardwar Pilgrimage in 1892, after previous low rainfall. It spread from India to south-east Europe in five months, against five years by the same route in the 1826–30 pandemic, owing to the greatly increased rapidity of communications. Maps illustrating the course of each of the above pandemics will be found in the writer's *Bowel Diseases in the Tropics.*

Endemic Areas and Epidemic Spread in India. For a century following the 1817 epidemic it was generally believed that cholera epidemics all spread periodically from the endemic area of Lower Bengal over India, and the well-known studies of the statistical officer,

Bryden, of 1869, with a series of maps based on army and jail figures, supported this view, and he also believed in the wind-borne theory of the spread of cholera. In a recent laborious study of all the available

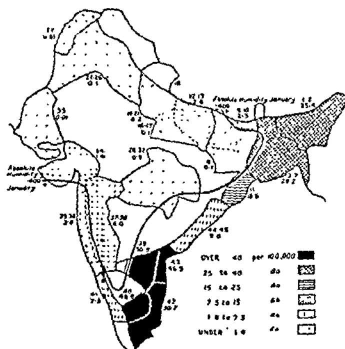


FIG. 45. Map of average monthly cholera rates in India.

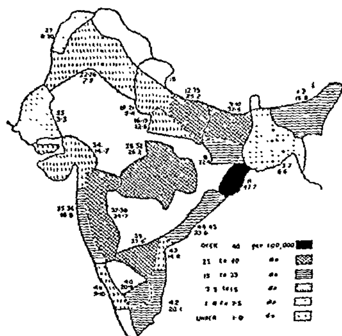


FIG. 46. Map of average monthly cholera rates in India during rainy season.

records of cholera for the past sixty years in each district of India the writer has shown that Bengal has not been the only home of cholera during the past half-century, for the 1875–77 epidemic spread from

three distinct endemic areas, which he defined, in which cholera has never been absent for a single year in three recent decades. They include, firstly, a very large north-east area comprising all Assam, Bengal, Bihar and the eastern divisions of the United Provinces ; this area is twice as large as the one defined by Bryden. Secondly, a large area comprising the central and south-east coast districts of the Madras Presidency ; and thirdly, the narrow, hot, damp Konkan coast of Bombay. These endemic areas are characterised by the continued prevalence of cholera throughout the winter months ; this prevalence *is related to the fact that the monthly absolute humidity never falls* for long below 0·400, and so is favourable to cholera all the year round. The absolute humidity first rises above 0·400 in the sub-Himalayan divisions of the United Provinces at the season of the annual spring recrudescence of cholera in that endemic area. In the remaining areas epidemics are liable to occur ; these include the Punjab, Central Provinces, most of the Bombay Presidency, and the elevated central portions of Madras, which are free from cholera in some years, and are subsequently re-invaded by epidemics from the endemic areas. The first introductions of the disease are nearly always brought about by pilgrims, who visit the endemic areas and bring back and spread *cholera in their own villages ; this is a point of great practical importance* from the prophylactic standpoint, as will appear later (*see* Figs. 45 and 46).

Climate and Cholera in India ; Forecasting Epidemics. A further study of maps showing the incidence of cholera in forty-five divisions for forty-five years, and charts showing the yearly incidence in each division, enabled the writer to trace the number of epidemics in each division and province in relation to the meteorological records, and also to trace the spread of the disease. He found that there were fewer epidemics in Lower Bengal than in the United Provinces, so that all those in the latter area could not all have spread from Bengal as *Bryden believed, nor did they occur in the same years in the different* northern provinces, but the Bengal curve differed widely from the curves of the provinces which lie to the west.

On working out the epidemics in various parts of India during the forty-five years, and comparing them with the rainfalls in the same areas, it was found that forty out of the forty-one epidemics had been preceded by failure of the rains of the previous monsoon or of the winter rains, or frequently of both, and the only exception was otherwise explained. It also appeared that an unusually early rise of the absolute humidity favoured early recrudescence or spread of epidemic cholera, and that by watching these two factors epidemic outbreaks can usually be foreseen several months before they appear. Correct forecasts have already been made on these lines by sanitary officers in India in the South Deccan in 1927, and the 1929 Sind epidemic also behaved in accordance with Rogers' rules. Moreover, a study of

forty-five yearly maps showing the epidemics in forty-five divisions of India and the frequency with which they occurred in neighbouring divisions in the same years confirmed the observation that cholera spreads from the three endemic areas already defined. Rogers has also reported the results of three successive yearly forecasts of cholera prevalence in fifteen areas of India with approximately correct results in the great majority of instances.

Pilgrims and the Spread of Cholera. The disease is spread by human intercourse; each year about *twenty million pilgrims* make long journeys in India to visit sacred, but often very insanitary shrines, and they frequently disseminate the disease over large areas. In some important places of pilgrimage especially large Kumbh gatherings take place every twelfth year. *It is very significant that the Allahabad* Kumbh Fair in January and February almost invariably results in serious cholera epidemics in the neighbouring divisions of Bihar and the east of the United Provinces, but not in the west of that province, where the absolute humidity is too low at that time of the year. Similarly the Kumbh Fairs at Hardwar have regularly caused epidemics in the neighbourhood west of the United Provinces and the Punjab every twelfth year from 1867 to 1927, except that the outbreak was comparatively slight in 1891, when the absolute humidity was exceptionally low and unfavourable to cholera at the time of the Fair in March and April. These epidemics occur in spite of the most elaborate sanitary precautions at the Fair sites; they even occur when there has been little or no cholera at the Fairs themselves, as at Allahabad in 1894, because they are essentially due to the movement of millions of pilgrims through, or to and from, the endemic areas. The Jaganath Festival at Puri and many others spread cholera whenever the disease is prevalent in their neighbourhood, and now that the dangerous seasons and years can be foretold from the climatic conditions, much could be done to reduce the enormous number of deaths from cholera in India which recently averaged 375,000 yearly, by inoculating the pilgrims against the disease either before or after starting on their perilous journeys, provided that this simple and effective measure is accepted by the Governments and peoples of the country. Many pilgrims were indeed inoculated on a voluntary basis on their return journeys in connection with recent Puri Fairs with promising results.

Progress in the Inoculation of Pilgrims against Cholera. The recommendations of the Indian Provincial Pilgrim Commission reports of 1913–16 did not make any reference to protective inoculation against cholera. *After the writer, in 1929, advised its use for the prevention* of the spread of the disease, the matter was considered by the public health authorities, who were unanimous against using it on other than a voluntary basis. In 1939 attention was drawn to the successful use of compulsory inoculation of some 100,000 pilgrims yearly going to

the Pandarpur Fair in the Bombay Presidency over a period of four years in controlling the former spread of cholera by them, and as the result of this success a committee of the Central Advisory Board of Health recommended the trial of compulsory inoculation at suitable pilgrim centres in each province of India.

Seasonal Incidence of Cholera. In Assam, Bengal and South-East Madras cholera increases in October to December owing to the absolute humidity remaining above 0·400 during the cold season. The disease decreases temporarily in Assam and Bengal in January and February, when the absolute humidity is nearly down to 0·400, but increases again from Assam to the east of the United Provinces in March, in the west of the United Provinces in April, and in the Punjab in May, with the rise of the absolute humidity to over 0·400 in each in turn. The disease is liable to be prevalent during the hot humid monsoon period of June to September all over India, except flooded Bengal and Assam, and it declines again in the autumn with the fall of the absolute humidity in North-West and Central India.

Although India is the great home of cholera, the disease is also endemic in Central and Southern China, with occasional epidemic prevalence there, and in the Dutch East Indies, Indo-China and Siam. There have been greater outbreaks in China in recent times than in India, but much less is heard of them owing to the absence of accurate reports.

Ætiology. Cholera is due to the comma bacillus (*Vibrio choleræ*), which was discovered by Koch in Egypt in 1883. It was soon shown by D. D. Cunningham, in Calcutta, that the comma-shaped vibrios found in almost pure culture in the stools of severe cases of cholera often showed great variations from the rigid cultural characters described by Koch, and it was not until the discovery of the agglutination test by Pfeiffer in 1894 that the difficulties in recognising cholera organisms were largely overcome. It is now accepted that the *pathogenic organisms cannot be distinguished by their morphological* characters from the numerous non-pathogenic saprophytic vibrios found in so many water supplies in warm countries, but true cholera bacilli are agglutinated in very high dilutions, such as up to 1 in 10,000, by the *serum of a rabbit which has received several intravenous injections of* the pathogenic organism, while harmless saprophytic vibrios can be *distinguished by their non-agglutination by specific sera (see* Coloured Plate, Figs. 63 and 64).

An elaborate investigation of J. Taylor, S. R. Pandit and W. D. B. Read helped to clarify matters, for they studied at least 1,000 different strains, including 558 inagglutinable vibrios which did not show the " O " antigen of typical agglutinable *V. choleræ*. By means of 33 sera they defined 31 serological groups of those 558 organisms, which they consider only include a fraction of those existing. Further tests with six sugars, the cholera-red and the Voges-Proskauer reactions separated

17 types, 13 derived from clinically cholera cases; so that inagglutinable vibrios show almost infinite variety, and they found little evidence of their causal relationship to cholera. They therefore came to the conclusions that (1) Vibrios of serological type differing from the true *V. choleræ* do not produce cholera; (2) observations made on the typical vibrios do not suggest that the inagglutinable strains can develop into the typical agglutinable form; this conclusion is in agreement with the results of prolonged investigations in cholera quarantine camps (p. 279), that epidemic cholera is only spread by acute cases caused by the typical agglutinating *V. choleræ*. Moreover, the occasional isolation of inagglutinable vibrios from patients during their convalescence from cholera, or from the healthy, affords no proof that they are ever the cause of the disease, for they exist so abundantly in nature that they may be expected to occur in the intestinal contents without being in any way related to cholera.

On culture the true agglutinable and non-hæmolytic *V. choleræ* tends to dissociate into smooth and rough colonies, both of which contain the heat-labile "H" antigen, but only the smooth ones contain the specific immunizing heat-stable "O" antigen, so these alone should be used in making vaccines for prophylactic use. A. D. Gardener and K. V. Venkatraman, from the close study of 100 races of cholera and cholera-like vibrios, found no reason to suppose that transmutation of species occurs under bacteriophage action at the end of epidemics. They also concluded that a standard "O" serum, together with the hæmolytic test, are necessary for the identification of true non-hæmolytic cholera vibrios.

The Cholera vibrio is a short, non-sporing curved rod 1·5 to 2 μ in *length and 0·35 μ in breadth, with a single terminal flagellum,* which differentiates it from many multiflagellate water vibrios. It stains readily with Ziehl-Neelsen's carbol fuchsin, gentian violet or Loeffler's methylene blue, and is Gram–negative. It grows well on solid media and liquefies gelatine to a variable extent. In peptone water it does not produce fluorescence or pigment, but on the addition of a few drops of sulphuric acid it gives the nitroso-indol cholera-red reaction owing to the formation of indol and the reduction of nitrates to nitrites; it usually ferments mannitol but not lactose. Cultures are polymorphic owing to the rapid formation of degenerative involution forms.

In severe cases a white flake from a cholera stool stained with carbol-fuchsin shows a nearly pure culture of vibrios: from such a flake direct cultures can be made on agar or other solid media. When the vibrios are scanty a loopful of the stool should be inoculated into a flask of 1 per cent. alkaline peptone water with a pH of 8 to 9, and incubated for about seven hours at 37° C. A loopful of the surface, where the vibrios multiply, is then inoculated on a plate of Dieudonne's alkaline blood agar; non-hæmolysing colonies are tested with a specific serum for agglutination. In examining a suspected water 100 c.c. of the

peptone solution should be added to 900 c.c. of the water and the same procedure carried out.

At the Egyptian cholera quarantine station at Tor in 1905 a strongly hæmolytic vibrio, known as the *El Tor* variety, was isolated ; this has caused much controversy. It has been frequently found in the stools of pilgrims to Mecca in the absence of cholera, but some hold that it may cause sporadic cases. A Celebes cholera epidemic of 1937 has been attributed to this organism, although it was not very strongly hæmolytic. It seems probable that the typical hæmolytic El Tor organism is not pathogenic.

Animal Infections. Research on this disease has been much handicapped by the difficulty in producing typical cholera infections in animals. Choleraic diarrhœa can be produced by feeding rabbits on the vibrios after neutralising their gastric juice, and more typical attacks are obtained in suckling rabbits in which there are few intestinal bacteria. Intravenous injections of large quantities of vibrios may also produce diarrhœa, with subsequent chronic infections of the gall-bladder as shown by E. W. D. Greig.

Cholera Carriers. Fortunately, the bacilli usually completely disappear from the stools of convalescent patients in four or five days, but Greig found virulent organisms in the stools of 36 per cent. of patients shortly before their discharge from hospital during an epidemic in Puri, so that the disease was rapidly disseminated by convalescents travelling by rail to the Central Provinces several hundred miles away. In Mesopotamia, F. P. Mackie and G. Trasler found that only 7·2 per cent. of cholera patients remained carriers of the comma bacillus for more than ten days after an attack, and only two out of several hundreds continued to be so up to five and seven weeks respectively, so that, fortunately, persistent carriers are far *fewer than after typhoid. Very similar results have been reported* from India and China. Isolation for two weeks from the onset of *the disease or for one week after convalescence is therefore advised.*

Prophylactic Examination of Immigrants and Pilgrims for Cholera Carriers. The discovery of the cholera vibrio naturally led to bacteriological examinations in quarantine camps, such as the very important Egyptian Station at Tor for the quarantine of all the Mahommedan pilgrims returning from Mecca by ship, in order to protect Egypt and Europe from the repeated invasions of epidemic cholera like those of the nineteenth century already mentioned. Quarantine camps can eliminate the really dangerous cases and carriers and are of immense value *in protecting Egypt and Europe from epidemics.* The origin of a severe outbreak of cholera in Egypt in October to December, 1947 was not traced. The Philippine Islands had for long been subject to cholera epidemics, but since 1934 only two isolated cases have occurred ; thanks to an elaborate system of stool examination of all immigrants, and isolation of vibrio carriers whether the organisms are agglutinable

or not. Similar measures have proved successful in recent years in protecting Japan from epidemics originating in China.

In Ceylon, too, some 100,000 quarantined immigrants from India were bacteriologically examined, with the following results reported by L. Nicholls. Altogether 84 agglutinating and 2,838 non-agglutinating cholera-like vibrios were isolated. Only the former are regarded as of any importance, for Nicholls found no evidence that the non-agglutinating vibrios ever gave rise to cholera, and the agglutinating strains rarely survive more than six to eight days. In the ten years a careful investigation of ten outbreaks revealed that in seven only one person was attacked, and apart from 305 cases in 1925, only 44 cases occurred in the ten years. Russell also records that extensive bacteriological research in India showed that most cases of cholera arose from previous cases, and in only 4 per cent. was there strong presumption that the source was a carrier. In the Dutch East Indies the remarkably low cholera rate in Java and Madura in the twelve years before 1934 is attributed by van Hunsel (1936) to quarantine operations, combined with large-scale inoculation and insistence on certificates of anti-cholera vaccination of immigrants and pilgrims. During these twelve years only 17 cases occurred.

Flies may play an important part in the dissemination of the disease by conveying comma bacilli from the stools to food supplies, especially to sweetmeats exposed for sale and to milk. The bacilli are conveyed both by the feet of the flies and by their excreta. H. E. Shortt, however, found that ingested cholera vibrios are either rapidly excreted or destroyed in the gut of flies, but they could readily be isolated from the fæcal and vomit spots of the flies up to eight hours after a feed.

Distribution of Cholera Vibrios in the Body. The extraordinary profusion of comma bacilli in the contents of the small intestine in the early acute stages of the disease is in striking contrast with their scantiness within the human tissues. They cannot be cultivated from the blood of patients, and can seldom be found microscopically in the tissues except in the occasional small pneumonic patches, in which they were demonstrated by Greig. The same worker succeeded in cultivating them in small numbers from the internal organs of fatal cases ; he also isolated the bacilli from eight out of fifty-five samples of urine, and in 30 per cent. of post-mortems he found them in the gall-bladder, which showed naked-eye signs of inflammation in 4 per cent. of cases. The numbers of comma bacilli in the tissues are thus extremely small as compared with the myriads which occur in the intestinal contents. It is, therefore, evident that the symptoms of the disease must be due chiefly to absorption of bacterial toxins from the bowels ; this view is confirmed by the experiments of Violle and Crenderipoulo, who caused fatal cholera toxæmia by the injection of peptone-water culture of the organisms into a ligatured loop of intestine.

Toxins and Antitoxins. Cholera vibrios produce both a soluble exotoxin and an endotoxin ; the latter is set free by lysis of the bacilli, which takes place to a great extent in the bowel. Lysis also occurs within a day or two in cultures. There are said to be two kinds of toxin, one a soluble thermolabile substance of a colloidal nature, which is antigenic and is neutralised by an antitoxic serum, and the other a thermolabile endotoxin formed in much smaller quantity and only one-fifth as toxic ; this is not neutralised by the antitoxic serum. H. C. Pham holds that the endotoxin acts on the abdominal sympathetic nerves, for small doses injected in the neighbourhood of the splanchnic nerve in rabbits and guinea-pigs produced symptoms resembling those of cholera.

Antitoxic serum was prepared in Paris and Russia as early as 1908–09 but did not prove effective in treatment. In 1936 Ghosn in Calcutta claimed a reduction in case mortality, but this has not been confirmed.

Anti-cholera Inoculation. As early as 1885 Ferran in Spain reported good results from the injection of living cultures of vibrios cultivated from cholera cases during an outbreak in Spain and in 1892 Haffkine used the same method in India with indecisive results. Soon after Kolle in Germany demonstrated the immunizing action in guinea-pigs of injections of carbolised dead organisms, which have ever since been widely used in India and elsewhere. Some failures have been recorded, which were probably due to true cholera vibrios not having always been used in preparing the vaccines before the specific Inaba and Ogawa types containing heat-stable " O " antigen were differentiated from the numerous strains of water vibrios.

When circumstances permit two doses of 0·5 and 1·0 c.c. of a vaccine prepared from true cholera vibrios are injected at a week's interval. Good results have been obtained in India from a single injection of 1·0 c.c. ; effective immunity results at the end of five days and increases up to ten days. Taylor showed that the vaccine will keep in a hot climate for two years and protection lasts for at least six months, which suffices to tide the subject over any period of epidemic prevalence of cholera.

Results of Prophylactic Inoculation. A general belief in India and elsewhere in the efficacy of the inoculations is confirmed by such examples as the following : in an outbreak of cholera in a large Bengal village Bentley recorded that at first only the Hindus submitted to inoculation and the disease ceased among them within a few days. The Muslim males then submitted to inoculation with a similar result, but cholera cases continued among the unprotected Muslim females until they too were inoculated, when the epidemic ceased ; this was a double control of a convincing nature. Examples of the control of cholera infections among inoculated pilgrims are also dealt with on p. 276.

Bacteriophage in the Treatment and Prevention of Cholera. The discovery that bacteriophages can destroy cholera vibrios in cultures aroused great hopes of their successful use in both the treatment of cholera and its prevention by distributing them in the water supplies during an outbreak. Unfortunately more than ten types have already been isolated each of which acts only on certain cholera vibrios leaving others unaffected. Polyvalent bacteriophages must therefore be used and in collapsed patients they can only act as adjuvants to more active treatment to replace the lost fluid and salts of the blood. Extensive trials orally have failed to yield conclusive results of their use in treatment. The distribution of polyvalent cultures in the water supplies during outbreaks have also yielded variable results. In Assam material benefits were claimed for this method of their use, but later inquiries have thrown doubt on the results owing to the absence of a strictly controlled basis for the tests. Trials in Bihar where the incidence of cholera is more uniform failed to yield evidence of the value of the addition of bacteriophage to the water supply, so it must be concluded that further carefully controlled trials during cholera epidemics are required to decide the value, if any, of bacteriophages in either the treatment or the prevention of cholera.

Other Prophylactic Measures. It was well said by Ernest Hart that "You can drink cholera, and you can eat cholera, but you *cannot* catch it." In fact, a well-managed cholera hospital is a perfectly safe place, but, of course, no food or drink should be taken in the hospital, and the evacuations of patients should be disinfected immediately and protected from flies. During cholera outbreaks no unboiled water or milk or uncooked food should be taken, and such things as salads should be prohibited. Aerated waters which have been kept for a few days are safe to drink. Chills predispose to cholera, so do saline purges, which should be avoided when cholera prevails. Fasting is also a predisposing factor, as shown by the frequency of the disease among Muslims during the period of the great Ramadan fast. Fright also predisposes to cholera by inhibiting the secretion of the gastric juice. Fly destruction, the protection of food from flies, and the control of the breeding places of these insects form an essential part of every campaign against cholera.

Plentiful application of D.D.T. should be made in the form of a dust to the breeding grounds, and of a spray to the places frequented by the flies ; the addition of pyrethrum to the spray ensures a speedy "knock down."

Disinfection of water supplies is another essential prophylactic measure which must be adopted on the outbreak of cholera, in addition to inoculation. It is remarkable how widespread the cholera vibrio becomes in the water of wells and stagnant rivers during cholera epidemics in the hot weather in India, which so commonly follow deficient rainfall, so that the supplies of drinking water are unusually

scanty at the time of outbreaks. In pre-railway days British regiments, travelling by boat up the Ganges in the dry cholera season, frequently contracted the disease by drinking the water of the slow-flowing shallow rivers. Tanks, which often form the only sources of supply of drinking water in Bengal villages also frequently become infected, as they are very liable to fæcal contamination owing to the insanitary habits of the vast majority of the people. Disinfection of the water supply thus becomes a matter of the first importance on the outbreak of cholera. The use of permanganate of potash for disinfecting wells, as first advocated by E. H. Hankin in the United Provinces, has proved a great boon to the country. For an ordinary well two ounces of the salt are placed in a bucket or other receptacle, which is then filled with water ; this is carefully poured off into the well, leaving the remaining undissolved crystals at the bottom of the vessel ; the process is repeated until it has all been dissolved. The water of the well should *be distinctly pink in colour if sufficient permanganate has been used.* The water of the disinfected wells can be drunk after a day or so without discomfort, when the remainder of the wells can be dealt with in a similar manner. A very extensive trial of this method over a series of years appears to have given good results, for in many instances striking and rapid decrease of cholera has followed its use. This chemical is usually too expensive for use in the case of large tanks, but fresh bleaching powder, or better, electrolytic chlorine, has been used with success in recent years for both tanks and wells, as it is far cheaper than permanganate and at the same time very effective. One of the most important means of conveying the disease is by the hands of persons who have attended cholera patients. The only way to break the chain of contact is by the use of disinfecting lotion for the hands of all who help to nurse cholera patients.

Quarantine of Far-Eastern pilgrims to Mecca at the El Tor camp in Egypt, with bacteriological examination of their stools, unless they had been vaccinated against cholera, has proved of great value in protecting Egypt itself and South Europe against invasion by sea.

Pathology. In persons who have died in the collapse stage of cholera the post-mortem appearances are characteristic. The subjects are usually well nourished, as the disease carries off the strongest in a few hours, the serous cavities are free from fluid and the pericardium often shows petechial hæmorrhages. The small bowel shows congestion of the peritoneal coat and great congestion of the mucous membrane, often with enlargement of the lymphoid follicles of the ileum. Extreme necrosis of the intestinal epithelium, with distension of the gland tubes with cholera vibrios, has also been described by D. N. Banerjee. The stomach and the upper part of the large bowel may show both congestion and petechial hæmorrhages. The lungs are dry and light in weight, owing to loss of fluid, and their blood vessels contain thick, dark blood. The gall-bladder is commonly distended with thick bile,

which requires considerable pressure to force it into the duodenum owing to the obstruction produced by great congestion of the bile duct and the duodenal mucosa. This obstruction to the flow of bile accounts for the colourless watery contents of the small bowel, which also contain numerous white flakes of desquamated epithelium. The loss of the epithelial lining of the small intestine mucous membrane accounts for the great drain of the body fluid and salts, which are given off in the rice-water stools during the acute stage of copious evacuations.

The kidneys show intense congestion and minute hæmorrhages between the tubules; it usually takes 80–100 mm. or more of mercury pressure to force saline fluid through the renal blood vessels after death, whereas 20–30 mm. is enough in persons dying of most other diseases. This shows that during the collapse stage the great congestion of the kidney prevents any appreciable circulation of blood through it, and so accounts fully for the suppression of urine during the collapse stage, as well as for the inevitable death from uræmia if the blood pressure does not rise to 100 mm. during the reaction stage which follows the period of collapse. The necessity for dealing with collapse as soon as possible is thus evident. Focal necrosis in the glomeruli and casts in the tubules were found in all fatal cases by D. N. Banerjee and S. K. Dutta.

The Blood Changes. The extremely rapid loss of fluid from the system in the acute stage of cholera is reflected in the blood changes which have been shown by the writer to furnish the key to the successful treatment. It has long been known that the great loss of fluid causes a rise of the number of red corpuscles to 7 or 8 million per cubic millimetre, and a relatively greater rise of the white corpuscles to produce a leucocytosis, usually of 15,000 to 20,000. This is accompanied by a *great decrease in the percentage of lymphocytes and a rise in the large* mononuclears, so that the proportion of the two is commonly reversed; thus cholera can be distinguished from arsenic poisoning in which *leucocytosis of the ordinary polymorphonuclear type occurs.*

The loss of fluid from the blood was measured by the process of centrifuging defibrinated finger blood in a hæmocrite in a series of cases. It was thus calculated that in mild cases of cholera not showing collapse the loss of fluid from the blood averaged 35 per cent.; in collapsed cases which recovered later after one or two intravenous saline injections it was 49 per cent.; in the worst cases ending fatally, in spite of salines, it was no less than 64 per cent., or practically two-thirds. The gravity of the cases was therefore in proportion to the loss of fluid, contrary to the earlier teaching of George Johnson. A more simple bedside method of estimating approximately the loss is by taking the specific gravity of the blood by means of a series of small labelled bottles containing mixtures of glycerine and water of specific gravities ranging from 1,050–1,070 by stages of 2 degrees. The set of bottles

can easily be made up in an hour with the help of a urinometer or specific gravity bulb. A drop or two of finger blood is drawn up into a capillary tube and a small quantity blown gently into the middle of the liquid in a bottle ; if it slowly sinks, the process is repeated with liquid of a higher specific gravity, until one is found in which it just floats for a second or two before sinking. This gives the right reading, while if it sinks in one and rises in the next, the intermediate figure is the correct one ; the whole test only takes a minute or two with a little experience. As the normal is 1,056–1,058, a rise to 1,063 indicates a loss of approximately 3 pints of fluid from the blood, one of 1,064 equals 4 pints, and 1,065 5 pints. The amount of saline injection required for transfusion is thus rapidly ascertained at any time. In patients who had been anæmic before the attack, the readings will be lower than in normal persons. Body-weight must be taken into account ; larger amounts are needed for large-framed heavy persons, and it is not desirable to adhere slavishly to the rule which has just been given.

The salts are also lost from the blood in large amounts ; this loss may even be greater than that of the fluid, so that the percentage of chlorides actually falls below the normal of 0·85 per cent., and in extreme cases hæmolysis may be taking place in the circulation. These cases are very grave, although recovery may take place if hypertonic saline injections are used. The salts have therefore to be replaced as well as the fluid, and experience showed that cases did better if the salt content of the blood was raised to above the normal—for example, to 1·0 per cent. An additional reason for using a hypertonic saline solution was furnished by Benjamin Moore, who pointed out that chlorides combine with the cholera toxins in the blood and cause them to be excreted through the kidneys. The rapidity of the relief of all the distressing symptoms of cholera by the use of these solutions also indicates that they counteract the pathological changes in the blood induced by the disease. The above blood changes were worked out by the writer in Calcutta in 1908–09.

Reduction in the alkalinity of the blood is yet another vitally important change produced in all severe cases of cholera from an early period of the evacuation stage. Sellards, in 1910, in the Philippines, pointed out that no amount of alkalies given orally in cholera sufficed to render the urine alkaline ; so he rightly inferred that acidosis is present and that alkaline injections are indicated to lessen the danger of post-choleraic uræmia, as Sellards showed to be the case. A little later, A. J. Shorten and L. Rogers, in over 100 cases, found a material reduction of the alkalinity of the blood in 79 per cent. of cases, including all severe ones ; they also found that when the reduction reached the high degree of N/100 fatal uræmia always ensued. These observations indicated the necessity for combating the acidosis by the administration of alkaline salines from the first to prevent the danger-point being

reached, as once it fell to below N/100 no amount of alkalies would avert a fatal uræmia.

The foregoing observations were confirmed in 1922 by M. Tsurumi and T. Toyoda, in Japan, as regards the occurrence of the reduction in the salts and alkalinity of the blood in cholera, and the value of the hypertonic and alkaline saline treatment described below in combating them. In 1941 H. M. Chatterjee and J. Sarkar found, in addition, that an increase of potassium and a diminution of serum calcium and of blood sugar may occur in cholera. Shortening of the coagulation time of the blood was found in most cases by S. C. Lahiri, and it roughly follows its concentration as shown by the blood specific gravity test. The modern treatment of the disease is mainly based on the observations of the blood changes. During the acute stage the alkalinity of the blood is usually from 7·5 to 8·5 *p*H.

CLINICAL DESCRIPTION

During an outbreak of cholera the cases vary greatly in their severity. At one end of the scale there are mild cases of diarrhœa, which would be regarded as " simple diarrhœa " if they occurred singly, and if no bacteriological examinations were made ; at the other end is the " cholera *sicca*," which fortunately is very rare ; in this the patient dies in a state of collapse before he has had time to pass a stool at all ; after death the small intestine is found to be distended with rice-water fluid, yet the large bowel may contain formed fæcal matter. Between these two extremes come the typical cases of varying severity ; in most outbreaks 95 per cent. of all the cases conform to the picture of typical cholera.

When cholera is prevalent every severe case of diarrhœa should be suspected to be one of cholera and treated accordingly.

Some authors emphasise the occurrence of a preliminary diarrhœa in which the stools resemble those of a simple diarrhœa at an early stage of the attack, but N. C. Macnamara, who had great experience of the disease, found this to be the exception rather than the rule in India, and as the early cases in an outbreak are usually of great severity, it is safe to say that the medical man will seldom be in doubt for any length of time as to the nature of the disease. It is towards the end of an outbreak that cases in which the stools are not characteristic are more common, and there are sporadic cases in which the disease cannot be diagnosed from the character of the stools ; some of these appear to be " flare-ups " in carriers of cholera vibrios.

At the onset, it is natural that the first stools should contain fæcal matter, but they quickly assume the rice-water character, in which they are watery, colourless, and contain little solid matter except flakes of desquamated epithelium. On standing, the flakes settle down to the bottom and leave a clear watery fluid above ; this [illegible]

mistaken for water, and Macnamara reported a case in which it had been drunk by mistake with disastrous results.

Collapse Stage. A striking feature is the copiousness of the evacuations, for a quart may be passed at a time, and several quarts may be evacuated within a few hours. It is, therefore, easy to understand the great concentration of the blood which takes place and is mainly responsible for the collapse and the disappearance of the pulse at the wrist. At the same time watery *vomiting* occurs, even when no fluid has been taken recently ; this may also amount to 1 or 2 pints at a time, and so aggravates the tendency to collapse. It is the combination of copious rice-water stools and vomiting which makes up the characteristic picture of the disease. There may be little or no pain at first in passing stools, which literally pour from the anus, but as collapse sets in and the pulse disappears at the wrist, severe *muscular cramps* begin to occur, due to diminished circulation of thick, highly-venous blood. The cramps begin in the fingers and toes and spread up the extremities, and may extend to the abdominal muscles. By this time the patient will have become cyanosed and very restless, the skin will be cold and clammy, and the axillary temperature may be only 95° F. ; there will now be complete cessation of urinary secretion and the respirations will be quick. The very dangerous collapse stage is now fully established, and such cases very rarely recovered before the modern treatment by hypertonic and alkaline salines and permanganates was commenced in 1908, and gradually improved during the next few years in Calcutta. With the modern treatment promptly and efficiently applied the great majority even of collapsed cases can be saved.

Reaction Stage. The algid stage may last from a few hours up to twenty-four or more, when it is not so severe as to prove fatal earlier, or when the collapse is tided over by effective treatment. It is followed by the stage of reaction with recovery of the pulse, cessation of the very copious evacuations, and return of warmth to the extremities with the revival of the circulation. If the algid stage has not lasted more than a very few hours, urinary secretion will now recommence and convalescence may soon be established, but in more severe cases in which the cold stage has continued for twelve to twenty-four hours, the reaction may be as dangerous as the former stage of collapse, owing to the frequent occurrence of severe toxæmia. This is due to renewed absorption of the toxins from the small bowel when the circulation is restored ; it is also common for the kidneys to fail to resume their functions, so that fatal uræmia results. Many experienced Anglo-Indian (old sense of the term) writers of the old school regarded the reaction stage as being quite as likely to prove fatal as the algid stage ; they had good reason for their belief as long as the older methods of treatment prevailed.

Febrile Reaction. The most striking and important feature of the

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urine should also have a fair specific gravity indicating the presence of urea and salts, and should contain little or no albumen. Low urea excretion and high albumen are bad signs.

Sequelæ. Under the old empirical and symptomatic treatment of cholera prolonged unrelieved collapse was frequently followed by sloughing of the cornea or gangrene of the fingers and toes, or of the penis and scrotum, but these have never been seen among nearly 2,000 severe hospital cases treated by the new methods.

Parotitis is another secondary septic infection of a serious nature which occurs in about 1 per cent. of cases, and it frequently goes on to suppuration, requiring early incision, but it also has become increasingly rare with the early use of saline injections.

Cholecystitis occurs in about 1 per cent. as a clinically recognisable condition, but it subsides rapidly and completely under purely medical measures, including local applications of heat.

Pneumonia is most common in cold climates such as Europe in the form of small broncho-pneumonic patches, which are often difficult to detect. It is a serious complication, associated with much toxæmia due to the presence of large numbers of comma bacilli in the lesions. These cases commonly terminate fatally within a day or two of the appearance of the lung trouble, and this complication accounts for a mortality of 3–4 per cent. in severe hospital cases.

Dysentery and diarrhœa may occur in the convalescent stage of the disease, but they yield readily to simple treatment. The passage of actual mucus has been noted in only about 1 per cent. of cases under the modern treatment, and no deaths have been seen. Diarrhœa also soon ceases without active treatment being required. Opium should never be given for these sequelæ, for fear of the far more serious uræmia.

Abortion and premature delivery are frequent in severe cases; sudden **cardiac failure** may prove fatal after slight exertion during early convalescence.

Hiccup of a very persistent nature may occur in the later stages but it is not of serious import.

DIAGNOSIS

The average case of cholera presents little difficulty in diagnosis especially as more than one case commonly occurs at about the same time and often in the same household. Mild cases, occurring chiefly at the end of an outbreak, are less characteristic, so that any doubtful diarrhœas which are seen at that time should be treated as probably choleraic, and, if bacteriological examination is practicable, it should be carried out to clear up any doubt. The following are the other forms of acute diarrhœa which have to be differentiated from *cholera asiatica* :—

Food poisoning often comes on as acutely as cholera itself and also produces serious collapse, so that when such a case occurs in an area

reaction stage is the rise of temperature with the recovery of the circulation and renewed absorption of intestinal cholera toxins. Indeed, this rise of temperature led Norman Chevers correctly to describe cholera as a fever in which the temperature is suppressed during the collapse stage. This view is confirmed by a recorded case in which during convalescence from severe cholera a smallpox rash appeared, for the initial smallpox fever had also been suppressed completely by the cholera collapse. Moreover, in a series of cholera cases in the Calcutta European Hospital, under the old methods of treatment without intravenous salines, during eleven years, the mortality was 81·6 per cent. Of the deaths, 62 per cent. occurred in the collapse stage, 15 per cent. died of post-choleraic uræmia, and the remaining 23 per cent. succumbed in the reaction stage from toxæmia and hyperpyrexia. In no less than nineteen of the twenty-two deaths in the reaction stage the temperature rose to 103° F. or over, including ten with the excessive temperatures of 105°–106·8° F., clearly indicating the great danger of excessive febrile reactions in this stage.

Post-choleraic Uræmia. The stasis of the renal circulation described under pathology, if of long duration during the algid stage, is liable to persist after the reaction has set in, and is as important as excessive febrile reaction in causing death at this period of the disease. It is frequently due to blood pressure not rising sufficiently high to restore the renal circulation and the excretion of urine: a rise to 80 mm. or thereabouts may be enough to cause a return of a fairly good pulse, but may not be enough to restore the secretion of urine, for which 100 mm. or more is usually needed in adult males. The result of a persistently low pressure will be fatal uræmia due to failure to overcome the stasis which occurs in the highly-congested kidney. These cases are by far most frequently met with in feeble Indian subjects of fifty years of age and upwards, in whom cholera is a most serious disease even at the present day. Another cause of deficient urinary secretion is a high specific gravity of the blood of about 1,060 to 1,062. This continued concentration of the blood to above the normal is sufficient to lessen renal secretion, although not sufficient to induce collapse; this condition can be detected by regular estimations of the sp. gr. of the blood, and is easily remedied. A very slight degree of chronic interstitial nephritis, requiring an abnormally high blood pressure to produce sufficient renal secretion in a healthy subject, is another not very rare cause of fatal post-choleraic uræmia; such fibrosis of the organ is met with much more frequently in fatal cases of cholera than in the general run of autopsies.

The urine should always be carefully measured and recorded twelve-hourly in all cases of cholera, and if after restoration of the pulse with the cessation of the algid stage less than 40 oz. are being passed in twenty-four hours, the measures described under treatment should at once be resorted to and continued until that amount is obtained. The

Army. In several thousand cases treated by the old methods in the villages of Bombay, the death rate in an epidemic of 1912 was recorded at from 51 to 60 per cent., but probably some of the mild cases were not returned as cholera.

The improvement resulting from the system of treatment described below may be seen from the fact that the mortality in the eleven years 1895–1906, inclusive, among 1,243 cases treated by the old method in the cholera wards of the Calcutta Medical College Hospital was 59 per cent., but among 1,429 treated by the fully-developed new methods from 1915–19 the death rate was only 20·8 per cent., or approximately one-third of the former rate. In the Calcutta European Hospital twenty-six successive cases were treated with only one death against a former mortality of 81·6 per cent. in the years 1895–1906.

In villages the full treatment is seldom practicable, but the use of permanganate pills in the Bombay Presidency caused an improvement in the results. In 1912 the mortality with the drug was 35·57 per cent. among 4,574 cases thus treated, against 51·64 per cent. in 11,599 untreated cases.

In collapsed cholera cases there is evidence that not more than 10 per cent. recovered in the Calcutta cholera wards under the old methods, but under the new treatment 68 per cent. of recoveries were obtained in collapsed cases treated with hypertonic salines and permanganates, and no less than 55 per cent. in patients admitted with no pulse at the wrist, whereas patients in this state scarcely ever recovered under former methods. These data show how great is the improvement in the prognosis when the modern treatment can be efficiently carried out. Among the Chinese, with greater resisting powers than most Indians, mortality rates of only 10–12 per cent. have been recorded in considerable numbers of cases.

The prognosis in individual cases is now favourable under proper treatment, except in feeble indigenous patients of over fifty years of age with collapse, and in acute cases in children under five years, who also have little resisting power. Bad features are collapse which has lasted for many hours before coming under treatment, with complete suppression of urine, rectal temperature much below normal, or very high, such as 103° F. in the collapse stage, with cold extremities indicating grave toxæmia, blood pressure remaining below 100 mm. in the reaction stage, hyperpyrexia and uræmia, with a blood alkalinity under N/80. Occasional outbreaks still occur in which the virulence of the disease is so great that a high mortality results, even though the modern treatment has been carried out.

TREATMENT

Historical. A century ago leading authorities in India used venesection even in cholera, and they also gave opium and calomel. In the middle of the nineteenth century George Johnson, in London,

where cholera is present, a correct diagnosis may be impossible until a stool is passed, when fæcal matter will be present, and a bacteriological examination, if practicable, will exclude cholera. There is usually also a history of several cases occurring almost simultaneously a few hours after a meal which has been taken by all the patients, whereas in cholera there is usually a longer interval between the onset of the cases. In this disease an immediate differential diagnosis is not essential to the correct treatment of a collapsed patient, the hypertonic saline treatment of cholera is equally indicated, and often proves very effective in severe food poisoning. As a rule the pulse remains perceptible and suppression of urine is usually absent.

Algid malaria, usually due to a malignant tertian infection, in which large numbers of the parasites are found in the capillary vessels of the intestinal mucous membrane, is of greater practical importance, as a successful issue depends on early correct treatment. As malaria of such a severe type rapidly produces anæmia, and this results in a fall of the specific gravity of the blood, the observance of the rule to make this estimation immediately on the admission of a suspected cholera patient will save the situation, as a fall instead of a rise in the density of a drop of the finger blood will be discovered. Further examination will lead to the discovery of malarial parasites and an increase of the large mononuclear leucocytes without the increase in the total leucocytes which occurs in cholera. By these simple means several cases of algid malaria have been rescued from the Calcutta cholera wards and their lives saved by anti-malarial treatment. In one such case there were forty-six parasites to every 100 red corpuscles in a patient who was admitted in a collapsed and semi-conscious condition.

Fulminant bacillary dysentery may also be mistaken for cholera as described under that disease (p. 264); this also is best treated with hypertonic saline.

Arsenic poisoning is not rare in India in the endemic areas of cholera, but the gastric symptoms and pain are usually more severe than in cholera, and the blood changes described on p. 284 will suffice to differentiate the two conditions.

Meliodosis may also produce severe diarrhœa and vomiting.

Moribund patients of all descriptions are liable to be admitted as cases of cholera during the prevalence of the disease, but a normal or low specific gravity of the blood will usually direct attention to the existence of some other cause for the patients' condition.

Prognosis and Mortality. In cases of cholera admitted to the large civil hospitals in India, which are more serious than the average village cases, the mortality under the old methods of treatment was 60–65 per cent. in Bombay, 59–63 per cent. in the Indian hospitals, and 81·6 per cent. in the European Hospital in Calcutta during a series of years. In the decade ending 1908 it was 54·2 per cent. among the Indian troops, 62·3 per cent. in jails, and 78·5 per cent. in the British

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advocated purging with castor oil, but his able pupil, N. C. Macnamara, found the treatment to be disastrous in practice. A. J. Wall, in his book of 1893, considered all forms of purging to be highly injurious; advocated opium and sulphuric acid orally in early cases, and morphia hypodermically during collapse, when no drugs are absorbed from the gastro-intestinal tract, but he recognised the danger of opium in the later stages of the disease with threatening uræmia. As early as 1831 Latta and Mackintosh used normal salines intravenously in Edinburgh, but had a mortality rate of 84 per cent. Wall also used this plan, together with subcutaneous salines, with a loss of over 70 per cent. of his cases. Koch's discovery of the comma bacillus led to the use of intestinal antiseptics without material benefit. The normal-saline treatment gave such poor results that it was seldom used at the beginning of the present century, and for ten years before the new methods were introduced only subcutaneous and rectal salines were being given in the cholera wards of the Calcutta hospitals, but the mortality remained high, as has already been mentioned. It will therefore be best to describe first the standard method worked out in Calcutta by L. Rogers between 1908 and 1915, with such a striking reduction of hospital deaths, and subsequently to refer to other methods of treatment.

Hypertonic and Alkaline Salines Intravenously and Permanganates Orally. The principles on which this system of treatment is based are very simple, for the fluid, salts and alkalies lost from the blood in cholera can be replaced most rapidly and satisfactorily by introducing them into the veins whenever a rise in the specific gravity of the blood indicates a serious loss of fluid. By the specific gravity test the necessity *for an injection of salines can be ascertained before* the patient has become collapsed if he comes under observation early enough, when prompt infusion may enable the collapse stage to be prevented, renal stasis to be relieved, and the danger of uræmia to be obviated. The administration of very large doses of permanganates is indicated by the demonstration by means of animal experiment that they can readily destroy the toxins of cholera bacilli by oxidation, and thus render harmless what would otherwise have been several times a lethal dose. The destruction of the toxins in the bowel strikes at the root of the pathological process, as it lessens materially their absorption into the circulation. To obtain the full benefits of this system of treatment the most assiduous attention of both doctors and nurses is essential, preferably in a special ward with all the necessaries ready at hand; so the treatment will be described in detail from the first steps to be taken on admission of a patient with cholera.

The majority of hospital patients are admitted after much fluid has been lost from the system, and they are already in a state of collapse, for this stage is commonly reached within two or four hours of the onset of the first symptoms of the disease. The following clinical points

will indicate the necessity for immediate infusion of salines : coldness of the extremities, little or no pulse at the wrist with a blood pressure below 70 mm. and especially cyanosis, restlessness and cramps. A. J. V. McDonnell considers that a difference between the systolic and diastolic blood pressure readings of under 20 mm. is an indication for a further saline injection. While the solution is being got ready the specific gravity of the blood and the rectal temperature should at once be taken, for the degree of concentration of the blood will indicate the amount of fluid to be injected by the rule already given. The rectal temperature is equally important for determining the temperature at which the fluid should be introduced to avoid a dangerously high temperature reaction when the restoration of the circulation, with renewed absorption of toxins from the intestine, is brought about by the saline infusion. In the early days of hypertonic saline injections these were followed by fatal hyperpyrexia in a few cases, and it should be remembered that once a cholera patient becomes unconscious from high temperature he never recovers, as the condition results from the absorption of a fatal dose of toxins from the bowel. This deadly complication was found to occur only in those whose rectal temperature was 102° F. or higher on admission. It is essential to know that hyperpyrexia, as shown by a rectal temperature of 108° F., may be present in a collapsed pulseless patient with cold clammy extremities, so this dangerous condition can only be detected by taking routine rectal temperatures on admission and every four hours during the collapse stage. If, therefore, the rectal temperature is over 101° F. the saline solution should not be warmed above the room temperature of about 80° F., which is common in the tropics. Since this rule was adopted, several thousand saline injections have been given without any patient being lost from hyperpyrexia. Whenever possible pyrogen-free recently distilled water should be used in preparing the salines. In any case, the fluid in the flask should never be above blood heat except in the rare and usually hopeless cases with a rectal temperature several degrees below normal, when the saline may be two or three degrees above blood heat to allow for cooling in the tube. A high rectal temperature may be reduced before giving a saline injection by means of an enema of 15–20 oz. of ice-cooled saline as advised by D. N. Banerjee.

Two solutions are used, the first being the hypertonic saline, consisting of 120 grains of sodium chloride, to which 4 grains of calcium chloride are added on account of the tonic action which it exercises on the heart ; the salts are added to 1 pint of sterile, distilled or pure water. The second is an alkaline solution consisting of 90 grains of sodium chloride and 160 grains of sodium bicarbonate to the pint of water. In order to avoid decomposition of the bicarbonate by boiling, it is sterilised in 160-grain packets in an autoclave or by dry heat and added just before use to the already sterilised normal saline. Each time that a patient requires a saline injection during the stage of

copious evacuations with a high specific gravity of the blood, 1 pint of the alkaline solution is first given, and the total quantity indicated is made up with the hypertonic solution, so that if the total is 4 pints, the first pint will be alkaline saline and the other three hypertonic saline. To lessen the incidence of temperature reactions after salines are given intravenously it is advised when possible to make up the solutions with distilled water that has been redistilled in an all-glass still in the presence of a few drops of sulphuric acid to make it faintly acid to litmus paper and a few crystals of potassium permanganate to give it a faint pink colour during the process.

The Insertion of the Cannula. It is necessary, in collapsed patients, to expose and open the median basilic vein to enable the cannula to be tied in, and even in patients whose veins can be distended it is seldom advisable to trust to puncturing the vessel through the skin on account of the large amount of fluid to be run in and the restlessness of the subjects. The patient seldom resents the small incision which is needed. The vein should be carefully cleaned of surrounding connective tissues, ligatured below, and a piece of silk placed around the upper portion and then looped twice. When the cannula has been inserted into the vein it can be gripped by tightening the loop without the necessity of tying a complete knot. The anterior wall of the vein is seized by a pair of dissecting forceps and a small oblique cut is made into the wall of the vein, using a knife or a pair of scissors. The incision is made just under the tips of the forceps. Slight traction by the forceps on the flap of the vein which is formed in this way will expose the opening into the vein and enable the tip of the cannula to be inserted. The silk loop, which is already in position, is then tightened over the vein and the cannula. If the opening in the vein is of the right size the cannula will fit snugly into it.

The rate of transfusion is regulated by means of a stop-cock near the head of the cannula, which is connected by rubber tubing with a narrow-necked flask whose openings can be plugged with cotton wool for sterilisation. The flask holds 1 pint, and is graduated with marks at every 2 oz. This simple infusion apparatus is made by Down Bros., and it is shown in Fig. 47. It enables the rate of flow to be regulated by turning on the tap after the cannula is tied into a vein, and then timing how long it takes for 2 oz. to run in, when the rate can be slowed or increased by adjustment of the stop-cock, and the flow again timed until the desired rate is obtained. In collapsed patients this should be about 4 oz. a minute, or a pint in five minutes, so that 4 pints can be given in twenty minutes ; if there is the slightest sign of oppression in the chest the rate should be slowed during the last pint or so of saline to about half the above rate.

In severe cases the relief afforded by the saline infusion is so great that the patient goes to sleep before it is completed. When the required amount has been given the cannula is withdrawn and at the same time

the ligature is drawn tight enough to close the upper part of the vein, but it is not advisable to tie it in a knot, because several infusions may be required in a bad case and the doubly looped ligature can easily be pulled loose so that the same vein can be used again within twenty-four hours or so. One or two sutures are inserted to close the wound, which

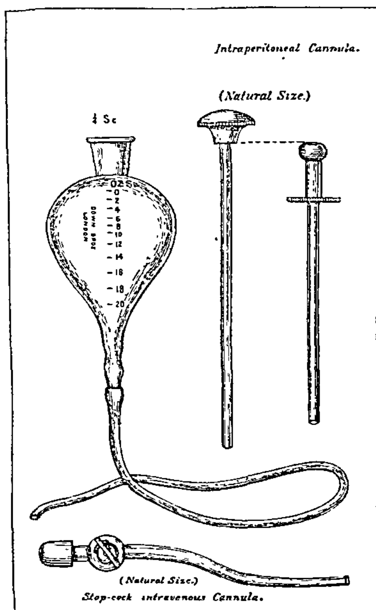


Fig. 47. Apparatus for intravenous and intraperitoneal injections.

can easily be opened by removing the sutures if the same vein is to be used again.

Repetition of saline injections is often required, and in all cases the blood pressure and the specific gravity of the blood should be taken morning and evening, and also whenever the patient is restless or does

not appear to be doing well, to determine whether further active treatment is needed. The saline infusion should be repeated whenever the specific gravity of the blood rises to 1,063 or over, and also whenever the patient passes large watery stools or shows renewed failure of the pulse or other unfavourable symptoms. There need be no fear of any harm resulting from repeated injections controlled by such observations, for an analysis of nearly 2,000 carefully recorded Calcutta cases proved that the reduction of the mortality for each year was in proportion to the average number of saline infusions given to each patient, and the best results were obtained in the year when the highest number were given, namely, 3·7 per case in 204 patients with a mortality of only 14·6 per cent., this being one-fourth of the old mortality in the same hospital. Injections for deficient urinary secretion described later were included in the number.

In young children intravenous salines can be given into the internal saphenous vein at the ankle or in the thigh, and even infants have been infused with the help of a fine-drawn-out glass cannula, or by the small cannulas used by physiologists for taking blood pressure curves in cats. Intraperitoneal hypertonic salines are also of value when intravenous transfusions are impracticable for any reason (*see* Fig. 47).

Treatment of Mild Cases not requiring Intravenous Salines. There remain the less severe cases in which the pulse and general condition are fairly good and the specific gravity of the blood is under 1,063. It has to be borne in mind that even in such cases the loss of fluid from the blood averages about one-third of the total amount, so that if diarrhœa continues the patient may rapidly pass into the more severe condition in which active treatment is needed to replace the loss of fluid. With a view to preventing this occurrence one-half to one pint of the alkaline isotonic solution unsterilised should be run slowly into the rectum through a tube ; the funnel should be raised only slightly above the body. This treatment should be carried out at once and repeated every two hours to combat the loss of fluid and the reduction of the alkalinity of the blood ; although part of the fluid may be returned with the stools, yet a good deal is likely to be absorbed, and the necessity for intravenous salines may be avoided in some cases. Water in small quantities at a time should also be given frequently by the mouth, in spite of some of it being returned through vomiting, and permanganates or kaolin may be added to the water, as described later, to lessen the absorption of toxins from the bowel.

The hypertonic salines may also be given subcutaneously or intramuscularly, but not the alkaline solution. The flanks of the thighs may be used for this purpose, and in females such injections can be given beneath the breasts. This procedure is more painful and less effective than the intravenous method and it is more likely to be followed by abscess formation in debilitated persons, even with careful antiseptic precautions.

The Reaction Stage. When the algid stage is terminated by the restoration of the pulse and surface temperature the *reaction stage* is reached. The temperature now rises above normal and must be closely watched, especially if the reaction is brought about by saline infusions. If the temperature reaches 103·5° F. cold sponging should be started to prevent the dangerous hyperpyrexia ; restlessness in these cases is often a sign of approaching danger. On the occurrence of the earliest sign of hyperpyrexia, and especially if the rectal temperature is excessive, *iced water enemata are indicated without delay. On the other* hand, continued low temperature during reaction is most unfavourable, as it is a sign of feeble vitality, such as is often seen in elderly patients attacked by cholera.

Alkaline Salines for Threatened Uræmia. It is in this stage that the greatest vigilance is necessary to avert the onset of the deadly post-choleraic uræmia, so the restoration of the urinary excretion must be closely attended to. If at least 1 pint of urine is not being passed every twelve hours the cause of the deficiency must be sought for ; it may be that the normal blood pressure has not been restored or that the specific gravity of the blood is still rather too high. In either case an intravenous injection of 1 pint of the alkaline normal saline is required, and this should be repeated as often as it is indicated by the signs just mentioned. Over 1,000 grains of sodium bicarbonate have been injected intravenously in the course of several days with success in overcoming prolonged suppression of urine with threatening uræmia. One pint of the alkaline saline should be given by the rectum every four hours until 40 oz. of urine are passed in the twenty-four hours, when it may be stopped. At this stage the diarrhœa usually ceases, and the patient enters on convalescence. No attempt should be made to check diarrhœa in either the algid or the reaction stages for fear of increasing the absorption of toxins. Sodium lactate is thought by D. N. Banerjee and S. K. Krishna to have some advantages over sodium bicarbonate for acidosis.

In cases in which the blood pressure in an adult male remains persistently below 100 mm., with resulting deficient urinary secretion, 1 c.c. doses of pituitrin solution should be injected two or three times a day, as this preparation is preferable to adrenalin on account of its more sustained action. Strophanthin may also be of value, as it is said to dilate the renal vessels while raising the general blood pressure.

Dry cupping over both loins should be used morning and evening as long as the urinary secretion is deficient.

Drug Treatment. Absorption from the bowel is in abeyance during the collapse stage, when the oral administration of drugs intended for absorption is of little use. Various intestinal antiseptics have also proved to be of little or no value. Great caution is required in judging the value of any drug in cholera on account of the great seasonal variations in the case mortality, which is considerably higher in the

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early hot weather at the onset of cholera prevalence than during the rainy season when the epidemic tends to decline in endemic areas such as its home in Lower Bengal. To enable reliable estimates to be made either alternate cases should alone receive the drug or its use should be continued for a year in an area in which the case mortality is known. The drug should be used in addition to the saline transfusions already described when the administration of these is practicable.

Permanganate of potash, in salol-coated or keratin-coated pills, was given by Rogers to over 2,000 patients in the course of ten years in Calcutta, in addition to hypertonic salines intravenously, with a further reduction in the case mortality and good results were also reported in China. Others have obtained good results from salines alone. Rogers had demonstrated by animal experiments that very small amounts of permanganate mixed with cholera toxins were harmless. He gave two 2-grain pills every quarter of an hour during the first two hours followed by two pills every half hour until the algid stage with copious evacuations had passed off. His results were confirmed by Maddock in outbreaks of cholera in Bombay villages, where salines were impracticable. He reported a case mortality of 33·5 per cent. in 4,547 cases under permanganates, against one of 51·64 per cent. among 11,599 control cases. The Government of India were thus led to supply permanganate pills for use in cholera cases in place of the old sulphuric acid and opium mixture, both of which constituents were found by Rogers, through trials in alternate cases, greatly to increase the mortality from post choleraic uræmia.

Kaolin is given in a strength of one to three in water, well stirred; it can be drunk in tumblerfuls to an almost unlimited amount, such as a pint every half-hour. Walker reported good results with it in China, he showed that it adsorbs the toxins but does not destroy the bacilli or the infectivity of the stools. It may also be given in the form of porridge made up of one pound of kaolin in a pint of water; of this, 3 oz. can be given every half-hour until vomiting and diarrhœa cease.

Atropine injected in doses of $\frac{1}{120}$ of a grain morning and evening during the collapse stage to lessen shock, as first suggested by Lauder Brunton, was tested in Calcutta by Rogers for a year in controlled cases, in addition to the hypertonic and alkaline salines, with a further fall in the mortality from 20 to 15 per cent.

Sulphonamides, chiefly sulphaguanidine, have been extensively tried in cholera cases and a further reduction in case mortality is claimed for their use. Most of the tests were uncontrolled so it is difficult to estimate their real value, but they are worthy of further trials especially under rural conditions not permitting of the efficient use of the saline treatment. Neither sulphonamides nor permanganates sterilise the bowels as regards cholera vibrios.

Chloromycetin has been found to inhibit *V. choleræ* in the intestines of white mice and so is worthy of carefully controlled trials in cholera.

Treatment of Complications. Pregnancy is a serious complication of cholera, because if the patient becomes collapsed the fœtus almost invariably dies rapidly of toxæmia and the mortality in the mothers is double that of non-pregnant cases even under the modern treatment. Lovell, in the Philippines, however, reduced the rate to that of other patients by watching for evidence of the death of the fœtus or the commencement of abortion ; he then removed the fœtus without an anæsthetic.

Pneumonia is treated by standard modern methods, but it is always a serious complication in cholera. Suppurative parotitis requires early incision ; this is usually followed by recovery. Penicillin can be expected to be valuable in this condition.

Diet. During the acute stages of cholera only water or barley water should be given, and kaolin or permanganates may be administered with it. This practical starvation is well borne for two or three days, except by feeble patients who are either old or very young ; to these glucose may be given in 2 per cent. solution either by the mouth or the rectum. It may also be given in saline injections if all food is rejected by the stomach, or as an isotonic, 4·5 per cent. solution intravenously, as it is a good food for the heart. Alcohol should always be avoided in the algid stage on account of its vaso-dilator action. It is useless to try to stimulate the heart when the fault lies in the great loss of fluid. During convalescence alcohol may possibly be of benefit in patients long accustomed to it, but it was never used in the successful Calcutta system of treatment.

Great care is necessary in commencing to give food in the later stages for fear of producing a relapse. It is better to err on the side of caution, and to begin with farinaceous foods such as arrowroot, cornflour and milk whey, but soups should be avoided until the kidneys act freely. The recumbent position should be enforced for several days to avoid sudden cardiac failure but convalescence is surprisingly rapid considering the severity of the disease.

L. ROGERS

CHAPTER XV

HILL DIARRHŒA AND SPRUE

HILL DIARRHŒA

Definition. Hill diarrhœa occurs at a height of 6,000 feet and over in the tropics during the rainy season; it is characterised by early morning watery white stools and flatulent dyspepsia; the symptoms are relieved by return to the plains, but if neglected may go on to the more serious disease—sprue.

Hill diarrhœa is common in the Himalayan hill stations of India, but may occur under similar conditions elsewhere during the humid rainy season, when it reaches its maximum prevalence. The disease was described by Alexander Grant in 1853; some of this observer's cases developed ultimately into typical sprue; it was also studied by A. Crombie in Simla.

The earliest symptoms are flatulent dyspepsia, with the passage of one to several stools from about 5 a.m. to 11 a.m. daily. The abdominal distension and flatulence are relieved for a time by the passage of the stools, but recur each morning. The stools are watery, frothy and nearly colourless, resembling whitewash, but they contain fæcal matter and are not offensive. As the flatulent dyspepsia may appear directly after the arrival of the patient in the hills, and in the early stages may cease at once on return to the plains, or even on going to a somewhat lower elevation in the hills, the disease cannot be due solely to an infection, but is rather a physiological weakness of the digestive organs in persons who may have been enfeebled by residence in the hot plains, and who are unable to withstand the sudden changes of climate involved by going to the cold moist atmosphere which prevails in the hills during the monsoon. Owing to the slightness of the inconvenience experienced in the early stages the affection is liable to be neglected, and it may then become chronic and intractable, so that a return to the plains may fail to arrest the trouble. There is a great risk of neglected cases going on to the more serious condition known as sprue; in one-fifth of fifty cases of sprue in Calcutta analysed by the writer their illness had commenced as hill diarrhœa. The absence of bile from the stools has been looked on as a sign of inaction of the liver, but the possibility of the bile having been converted into colourless leucobilin, as in sprue, must be remembered. The disease may recur yearly and produce wasting in people who migrate annually to the hills.

Crombie pointed out that every gradation is seen in people arriving in a hill station between mild flatulent dyspepsia and persistent hill diarrhœa. By no means everyone going to the hills is attacked, and

doubtless any constitutional weakness of the digestive powers is likely to predispose to its occurrence. Grant noted also that the intemperate are more severely affected than the temperate, although the latter are by no means exempt.

The prognosis is far more favourable than in typical sprue if the patient has not become debilitated through neglect of the disease, and if he moves at once to the plains or to a considerably lower elevation. A return to the hills should be avoided; the patient should go to Europe for the hot season if a change of climate is required.

Treatment

In the early stages simple treatment is often effective, but if it fails to control the diarrhœa the patient should at once be sent to a lower elevation. Grant recommended a dose of blue pill followed by a Dover's powder at bedtime; in the morning an ounce of castor oil with a little laudanum is given. He pointed out that opium should not be given without being combined with ipecacuanha for fear of its deleterious effect on the liver. A. Crombie considered the disease to be primarily due to defective gastro-intestinal secretion and chills; he found that 10 grains of pepsin two hours after meals relieved mild cases, and that *liquor hydrargyri perchloridi* in doses of one drachm fifteen minutes before meals was a useful intestinal antiseptic. Bismuth salicylate in 20-grain doses about two hours after food three times a day as long as diarrhœa continues is of value in checking intestinal fermentation and flatulence, as in sprue, and as the symptoms subside the doses are gradually reduced to only one in the evening.

The diet should consist of milk in small quantities at frequent intervals; in severe cases peptonised milk may be required for a time. Protection of the abdomen from chills by a flannel binder, especially at night, is an essential measure. Such simple methods commonly suffice to remove the trouble, and their success bears out the view that in its early stages hill diarrhœa is but a temporary derangement of the gastro-intestinal system and is not due to any specific organism.

SPRUE

Definition. A serious form of chronic diarrhœa occurring in persons who have resided in warm climates. It is characterised by colourless stools, deficient absorption of fats, and sore tongue and mouth; it is often complicated by macrocytic anæmia.

Historical. As early as 1776 Hillary described the disease as seen in the West Indies under the descriptive term of "diarrhœa alba," but it is now known as sprue, a term of Dutch origin. It was described in 1853 in India as "white flux."

Distribution. It is found chiefly in China and Indo-China up to Korea, in the humid coast towns of India and Ceylon, the East and West Indies, in the Southern United States, Southern Italy, and in

Queensland; all of these places have hot, damp climates producing debility. Tropical Africa appears to be nearly free from the disease, and light might be thrown on its ætiology if the reason of this striking immunity could be discovered.

Ætiology. There have been many speculations in the past regarding the true nature of this disease, but increasing knowledge of the physiology of the small intestine and of biochemistry has thrown considerable light on the problem.

Deficient absorption of fats from the small bowel has for long been recognised as a characteristic feature of sprue. This can be accounted for by thinning of the mucous membrane due to atrophy of the valvulæ conniventes, through the lacteals of which fat is absorbed. Conditions resembling sprue include cases designated non-tropical sprue, steatorrhœa and cœliac disease; all characterised by deficient fat absorption. Moreover, it is significant that the elimination of the absorptive action of the small bowel, by anastomosis of its upper part or of the stomach with the large gut, produces symptoms resembling to a great extent those of sprue.

When we consider the causes of the deficient fat absorption in sprue the matter is more theoretical and complicated. The presence of bile salts and acids in the small bowel materially assists the absorption of fats; in sprue they are either deficient in quantity or the bilirubin is converted into a colourless substance: hence the white colour of the stools. The degree of deficiency of fat-absorption in sprue, and methods of raising it, have been studied by means of fat-tolerance tests. Nissen's test shows that when after a twelve-hour fast a dose of 1 gm. per kilo body-weight of butter fat is given the lipoid in the blood serum five hours later is much less in sprue than in control cases. Black found great daily variations in fat absorption, but averages over several days showed decreased absorption amounting to about 50 per cent. in cases with loose stools and to 24 per cent. with formed ones. Researches on the effects of administering liver extracts, vitamins and the more active constituents of yeast preparations such as "Marmite" and "Vegamite" on fat absorption have also yielded important indications for the treatment of sprue. Thus the prolonged administration of liver extract and of vitamin-B complex from yeast products raises the average fat absorption in sprue to above the normal level and injections of the less purified liver extracts raise the fat and glucose curves to nearly the normal level. The addition to the diet of 10–15 gm. of commercial lecithin or phosphorlipids materially increases fat absorption both in sprue and in normal subjects. On the other hand the administration of nicotinic acid or riboflavin does not improve fat absorption, but the former is reported to be of value in relieving the painful glossitis. Spies and his colleagues found that the yeast product, folic acid, is rapidly effective in relieving symptoms of sprue, so it can be combined with liver extract with advantage.

Thus the whole tendency of recent work has been to stress physiological and dietetic deficiencies as the essential causes of sprue and closely allied conditions. Former suggestions that infections with monilia fungi and oral streptococci, so abundant in the ulcers, played an important part in the causation of sprue have received no recent support.

A reduction in active ionic or free calcium, but not of the total calcium, in the blood of sprue patients has also been demonstrated, but Scott's treatment of sprue by the administration of parathyroid and calcium appears only very occasionally to be of value.

Pathology. Apart from emaciation, thinning of the mucous membrane of the duodenum and jejunum is the only frequent morbid change met with in sprue at autopsies performed early enough to exclude post-mortem changes. Small superficial ulcers of the small intestine have occasionally been recorded but are quite exceptional. The tongue and œsophagus commonly show a raw red appearance due to loss of the superficial epithelium together with the presence of superficial ulcers, the gastric mucosa may show atrophic changes and in cases with acute diarrhœa the rectum and sigmoid may show patches of superficial inflammation. The liver is atrophied and may be only half its normal weight, and enlargement of the mesenteric glands has been recorded. Emaciation is well marked in fatal cases. The sternal marrow often shows changes similar to those of pernicious anæmia with an increase in the number and size of the megaloblasts.

Clinical Description

Onset. The first symptom of sprue is almost always persistent diarrhœa, which, in India at any rate, nearly invariably precedes the mouth symptoms by several weeks. The stools soon become very light-coloured or clay-like, and are voluminous, frothy from gas formation, and soft or pasty in consistence. If the stools are numerous weight will be lost rapidly. The disease varies greatly in its acuteness, from mild cases in which there is little more than chronic flatulent dyspepsia, with one or two soft stools a day and no other characteristic symptoms, to acute attacks with several stools daily. In severe cases the typical soreness of the tongue soon appears, and the disease is then sometimes called complete sprue, as opposed to the incomplete disease in which only bowel symptoms occur.

Progress. The untreated disease usually runs a variable course, with alternate exacerbations and remissions of the symptoms, and in typical cases it is usually noticed that any increase in the soreness or ulceration of the tongue and mouth is very soon followed by an increase in the diarrhœa, as if there were a spread of the inflammation of the mucous membranes down the alimentary canal. During the intermissions of the more active symptoms the patient may feel better and

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X-Ray examinations show no evidence of ulceration of the bowel. After a barium meal the normal feathery appearance of the duodenum and jejunum is absent as the result of atrophy or flattening of the valvulæ conniventes. This reduces the absorptive surface of the mucous membrane.

Increase in the Intestinal Fatty Acids. Another change in sprue patients is that the proportion of fatty acids to neutral fats is increased from the normal of two to one up to four to one or five to one. Deficient absorption of fats from the small bowel is indicated by the fact that the total weight of fatty acids and neutral fats in dried stools varies between 25 and 50 per cent.; this failure of absorption appears to be the important cause of emaciation rather than a deficiency in the digestion of fats.

Light was thrown on this subject by the observation of Barker and Rhoads that in sprue patients there is an absence of the normal increase of lipoids in the blood following a fat meal, as the result of failure of fat absorption in sprue. Moreover, after treatment by intramuscular injections of liver extract in some of the cases there was a marked rise in the lipoid absorption to approximately normal, combined with a temporary cessation of the bulky stools containing excess of fats. They therefore considered that mal-absorption of fats is the cause of the diarrhœa in sprue, as pointed out under ætiology.

The diminution in the liver dulness in sprue is due partly to atrophy of the organ and partly to the distension of the bowel with gas, which tends to obscure the liver. In the early stages there may be some temporary enlargement of the liver.

Diarrhœa is the most constant and important symptom of sprue. In the acute stages the stools may be watery, but much more frequently they are only loose or semi-formed in consistency; they are often frothy from the presence of gas, and the most characteristic feature is their very pale-yellow or almost white colour, due to the alteration of the bile pigment into colourless leucobilin. Even when the evacuations become solid and formed they still remain pale for some time, and the gradual change to the normal brown colour is one of the surest signs of approaching recovery. Owing to the amount of fats present the stools have a low specific gravity and float in water. They also contain small bubbles of gas, due to fermentative changes; this accounts for the persistent flatulence, especially in the early morning.

Just as in hill diarrhœa the stools are passed chiefly in the early morning, and their passage affords relief to the abdominal distension and discomfort. The number of stools varies greatly in different cases and at different periods in the same case. In the milder cases, after the passage of two or three loose or soft stools in the morning, the patient remains free from further trouble during the rest of the twenty-four hours, but in severe cases other evacuations may recur later in the day, and the total may rise to seven or so daily. In these severe

even gain a little weight, but they are usually short, and the general tendency is for the disease to progress fairly steadily, especially if the patient is tempted by a temporary improvement to relax in the least degree the dietetic and other precautions. Emaciation and weakness also tend to progress with each return of the symptoms, and sprue commonly runs a very chronic course, usually extending over several years. Some cases run a more acute course ; in a Calcutta European Hospital series of forty-five cases, five out of six deaths took place between six and twelve months after the onset of the disease.

Terminations. In the more acute types, seen chiefly in patients remaining in the tropics, the diarrhœa continues in spite of every care with the diet, and the patients eventually succumb to exhaustion. In patients over forty-five years of age a severe pernicious type of anæmia is liable to occur and to prove fatal within a few weeks if not treated radically without any delay. In other more chronic cases, especially when the patient has not sufficient patience to submit to prolonged and strict dieting, relapse after relapse takes place, with increasing emaciation and weakness, until fatal exhaustion ensues. Tetany may be met with in the late stage, apparently from exhaustion of the parathyroids. Such is the general course of sprue, and we may now turn to a fuller description of some of the main features of the disease, a knowledge of which will help in its treatment, commencing with the alimentary system from above downwards.

The tongue and mouth lesions are among the most characteristic features of fully-developed sprue, but they vary considerably in their degree, and during the earlier intermissions of the disease they may be nearly or completely absent, so a diagnosis of sprue cannot be excluded on account of their not being evident. During exacerbations the tongue shows patches of congestion, especially at the tip and edges, giving it a red, raw appearance, and often accompanied by superficial erosions or small vesicles ; similar changes may be present in other parts of the mouth, and the inner surfaces of the lips and the palate. These changes are accompanied by tenderness and pain on taking any salt, hot food, spices, wines, etc. Small ulcers are often seen which are also very painful, and from any of these lesions pure cultures of streptococci can commonly be obtained. Not infrequently there is pyorrhœa associated with the presence of the same organisms ; this may be a further source of secondary streptococcal infection. During the intervals between the exacerbations of the mouth symptoms the tongue presents a smooth, raw appearance owing to the denudation of the superficial epithelial layers, and cracks may appear on the dorsum of the organ.

With an increase in the soreness of the mouth the same symptoms may be present on swallowing, indicating the presence of similar changes in the œsophagus ; these also wax and wane with the variations in the intensity of the general alimentary symptoms.

resistant to treatment the patient should be sent to a cool climate, but not to a hill station in the tropics. With prolonged careful treatment recovery is then the rule, except sometimes in elderly patients in whom there is early or rapid development of anæmia ; in these cases the prognosis is often grave. Equally unsatisfactory are patients who leave off treatment and strict dieting as soon as a little temporary improvement appears, for they are likely to develop a very intractable chronic form of sprue of several years' duration, to the increasing weakness and emaciation of which they eventually succumb after many ups and downs. Progressive loss of weight with emaciation, long-continued frequency of the stools, great soreness of the mouth, interfering with feeding, frequent exacerbations, followed by increased diarrhœa, and a severe degree of anæmia are all serious symptoms. On the other hand, *favourable symptoms are decreased frequency and better consistency* of the stools, with a gradual return towards the normal colour, and steady gain in weight towards the normal level, especially if all these are maintained over a period of many weeks or months with only slight temporary setbacks, which are almost inevitable. An essential point is that sufficient patience must be exercised to enable the good effects to be consolidated before any attempt is made to return to a normal diet and mode of life. Given such conditions, complete recovery, as far as regards the maintenance of good health in a cool climate, may be expected in the great majority of sprue cases which come under observation before very serious deterioration of the health has been produced. In young and vigorous subjects the cure will usually be sufficiently complete to justify a return to the tropics with a prospect of continued good health, but this is not desirable in persons beyond middle life, in whom recurrence, with grave danger of severe anæmia setting in, is much more likely to occur.

Treatment

Dietetic. The first essential measures in well-developed cases are absolute rest in bed and prolonged milk or high-protein diet. To allow sprue patients to go about, or engage even in housework, only too often results in the disease becoming chronic and intractable ; whereas prolonged rest and strict dieting for several months often brings about a rapid gain in weight and strength and subsequent steady convalescence and that, too, even in patients who have suffered from repeated relapses extending from one to several years on less drastic treatment. The longer the previous duration of the disease the more prolonged must be the period of complete rest which is required for the body in general, and for the digestive system, if a lasting recovery is to be achieved. Given, however, the necessary conditions the treatment is generally satisfactory in the end. It will be best, therefore, to deal fully with dietetic measures in the first place and subsequently to discuss the use of drugs in the treatment of sprue.

cases there is rapid emaciation and increasing weakness if the diarrhœa is not stopped. Under a rigid diet the number is soon reduced to one or two a day, but the smallest addition to the diet is likely to bring on a relapse, and great patience on the part of both the patient and the physician is essential if complete recovery is to be brought about. In no other disease is it truer that "the more haste the less speed." The great bulk of the evacuations is another characteristic feature of sprue; this is due to the undigested nature of the stools, and is a sign that the disease is not yet under complete control. Drugs, such as bismuth and iron will make the stools dark in colour, so if they are in use they should be omitted from time to time to allow the natural colour of the evacuations to be observed and the progress of any improvement in this respect to be noted.

Anæmia is a common complication of sprue; it is liable to assume a severe degree and even a pernicious type in long-standing cases. In persons of forty-five years of age and upwards it may develop and prove fatal within a few weeks; in these cases normoblasts are found in the blood. The resemblance of sprue anæmia to the pernicious forms has frequently been noted, as both show a high hæmoglobin index, and Fairley and Mackie state that it differs from pernicious anæmia in being a non-hæmolytic megalocytic type with low Van den Bergh readings and increase in the size of the red corpuscles. The Arneth count has been reported to differ little if at all from the normal.

Diagnosis is rarely difficult in well-developed sprue, because the combination of the characteristic chronic white diarrhœa and sore tongue cannot well be mistaken for anything else, although the diarrhœa of pellagra may also be accompanied by soreness of the mouth. When the mouth symptoms are absent in the so-called incomplete sprue the bowel symptoms alone suffice for making a correct diagnosis, and it is important to recognise them as early as possible in the disease, as treatment will then be much more satisfactory than after repeated attacks have caused serious deterioration of the general health. The large proportion of fatty acids in the stools is a diagnostic point of great importance when an analysis is possible. Even when the stools are not characteristic in appearance it is best to suspect early sprue in all cases of persistent diarrhœa which cannot be accounted for in any other way. Any unexplained tropical diarrhœa of more than ten days' duration should be treated as sprue, provided amœbic and bacillary dysenteries are excluded.

Prognosis is more difficult than diagnosis, as cases vary so much in their severity, from a mild looseness of the bowels accompanying flatulent dyspepsia and yielding readily to dietetic care, up to occasional cases of an acute type of typical sprue with rapid deterioration of the general health in spite of treatment, and causing a fatal result in six to twelve months after the commencement of the disease. The mildest cases may recover even in a tropical climate, but if the disease is at all

Bombay, preferred buttermilk, beginning with 2 pints and gradually increasing up to seven.

Additions to the milk diet may be made very cautiously at the end of about four to six weeks, if the stools have become solid and the soreness of the mouth has cleared up, but if any definite set-back results, pure milk should be reverted to. Lightly boiled eggs may now be well borne and rusks or toast may be given, and if such starchy foods are well digested a little stale bread or toast should be tried, the patient being instructed to masticate all solid food very thoroughly. Broths may now be given, and "Marmite" added, as it contains much vitamin B, and this often leads to a more rapid gain in weight at this stage of the progress of the case. Fruit, in the form of ripe bananas or strawberries, if in season, can next be given; the value of the latter, which has been over-rated, being probably due to the vitamins which they contain. If the patient is still gaining weight and is free from intestinal symptoms, and if the stools are getting back towards their normal colour, fish and then chicken are next added to the diet. The patient will have been at rest in bed in a warm room throughout the milk treatment, and during the early additions to his diet, but he may now begin to get up, but should be warmly clad and wear flannel round his abdomen to avoid any chill, which is liable to produce a return of bowel trouble. When he has regained all, or nearly all, the weight lost during the active progress of the disease, and the stools remain both formed and of a good brown colour, he may proceed to a warm place, by the seaside for choice, to convalesce, but he should certainly not return to the tropics for six to twelve months after complete recovery, and then only in the cold season. It may be well to spend the winter in a mild climate such as the South of France or South Devon or Cornwall if he is not yet fit to return to the tropics.

High Protein Diet of Fairley. It has long been known that fats and excess of carbohydrates are not well digested by sprue patients, and N. H. Fairley has worked out a scientifically based diet on these lines with the advantage of personal experience of the disease. His five diets provide gradually increasing quantities of food as the patient progresses, with an advance every two to four weeks in severe cases, and may be summarised as follows. No. 1 consists of meals at 8 a.m., 12 noon and 6 p.m. each composed of underdone beef 3 oz., rusks ¾ oz., glucose 1 to 2 drachms and the juice of half an orange, with the addition to the midday meal of 4 oz. soup plus the extract of ⅝ lb. of liver. Its calories total up to 770 with protein, fat and carbohydrate in the proportions of 1, 0·3 and 1·2. In No. 2 diet the beef is increased at each of the three meals to 5 oz., the rusk to 1 oz., the glucose to 2 drachms and the orange juice to double, with the addition of calves-foot jelly 2 oz. at two meals, and tea 10 oz. and milk 2 oz. in the afternoon. In No. 3 the beef is increased to 6 oz., the rusks to 1½ oz., at each meal, and one baked apple with 1 oz. custard is given at 10 a.m. and with

Milk Diet. When we recall the congested condition of the intestinal tract it is evident that the prolonged use of the simplest and most easily digested and absorbed diet is essential to give the necessary rest to the diseased mucous membrane, so as to allow time for the subsidence of the pathological processes and the gradual restoration of the functions of the bowel. A good diet is milk, which is the nearest approach to the natural food of delicate infants. It is only in rare cases that any serious difficulty is met with in getting the patient to take a pure milk diet although he may object to it at first; in most cases, 3 pints can be taken in twenty-four hours in small quantities at a time and sipped slowly, by teaspoonfuls if necessary. During the first week or so the patient generally loses a little weight, but this is of no consequence, and it is more than compensated for by the decrease of abdominal discomfort and flatulence and by the diminution in the number and bulk of the stools. The daily amount of milk should be slowly but steadily increased by half a pint every few days, as long as it is digested without trouble, and when five or six pints can be taken daily the patient almost invariably begins to gain weight fairly steadily. He should be warned that there are certain to be ups and downs owing to slight exacerbations of the intestinal trouble from time to time, but these should be regarded as indications that it is still necessary to continue a strict diet. As long as the general progress is satisfactory, apart from these occasional variations, the desired result is being slowly attained, and it is advisable to leave well alone and not be tempted to increase the diet too soon, as nothing is more easy than to produce a decided set-back, which will retard materially the ultimate recovery.

A modification of the milk diet, on the lines of the high protein diet described below, is the use of "Sprulac" made by Messrs. Cow and Gate at the suggestion of Fairley, in a convenient powder form containing protein 34 per cent., lactose 45 per cent., fat only 10·6 per cent., mineral matter 7·4 per cent. and moisture 3 per cent., with a caloric value of 125 per ounce. It only requires to be dissolved in hot water in accordance with the directions, and given every two hours during the day up to six meals, the total quantity being gradually increased from two to three pints up to five or six, with total calorie values of 700 to 2,500. The writer has found this preparation of great value in sprue patients from the tropics who were not ill enough to require hospital treatment, and it should be specially useful in the tropics where the more complicated high protein diet may not be so easy to carry out. G. E. Brooke considers pancreatised "Peptolac," of the same firm, better than Sprulac.

In order to vary the monotony of this diet, Benger's food, which is already digested, may be substituted for some of the milk feeds. Some prefer skimmed milk to lessen the ill-digested fats, and 1 oz. of casein may be added to each pint to increase its nutritive value. Rele,

produces clinical and hæmatological improvement. The dosage suggested is 30 mg. daily for ten days, 20 mg. daily for ten days and thereafter a daily maintenance dose of 5 mg.

The cobalt-containing red vitamin B_{12} given in such minute dosage as 100 μg. daily by injection produces a rapid clinical improvement.

In using liver extracts by injection it must be realised that large numbers of inert extracts are offered for sale in tropical bazaars ; it is essential to use products of firms who care for their reputations. Even the finest liver extracts may produce serious or even fatal allergic reactions if used over a prolonged period.

The actual treatment advised will depend (outside Great Britain, where all drugs are obtainable free) on the financial capacity of the patient, hospital, or dispensary and on the current price of the specific products.

A sound procedure is to commence treatment by injecting 4 ml. of " Anahæmin " twice weekly reinforced by 100 μg. of vitamin B_{12} and then to pass on to maintenance doses of folic acid by mouth when the clinical and hæmatological pictures are satisfactory.

When convalescence has become established by the use of combined dietetic and specific replacement therapy health may be maintained by the use of a high protein diet, the routine administration of multi-vitamin tablets and a daily pill containing folic acid. In Great Britain extra rations of red meat are available for sprue patients.

LEONARD ROGERS

the afternoon tea, and the tea and milk is also given at 6 a.m.; the total calories now being 1,820. In No. 4 the beef is increased to 7 oz. at a time, the liver soup to 5 oz. and the custard to 5 oz. totalling 2,200 calories. In No. 5 butter 1 drachm and honey 2 drachms are added at two meals, and a lightly boiled or poached egg may be *substituted for custard, with a total of 3,200 calories.*

When a sprue patient becomes convalescent under the above diets any of the following may be added gradually: underdone lean chop or steak, boiled or steamed filleted fish, thin toast, stewed fruit, jam, cooked liver, chicken, cold meat without fat, and sweetbread. Among vegetables, spinach, marrow, cauliflower, French beans, onions, young peas and small amounts of boiled potatoes may be allowed. Also junket, milk jelly, Canary bananas and other fruits. Madeira or sponge cake, Marie or water biscuits. Foods to be avoided include salmon, cheese, new bread, marmalade, suet puddings, fatty foods, nuts, pastry and alcoholic drinks.

Fruit has been much advocated in sprue; in both India and the West Indies ripe bananas have been found to be of value. The Dutch rely largely on apples, but in Great Britain strawberries are favoured, given in quantities gradually increased up to two or three pounds daily. Fresh bael fruit may also be of use in countries where the fruit grows, but the dried preparations are of little or no value.

It is sometimes necessary to ring the changes in the dietary, as a diet which suits one patient will often disagree with another, and sometimes a diet which has suited a patient at one stage of the disease will be found to upset him later on.

Drug Treatment. Relief from particular symptoms may be obtained by the exhibition of such standard remedies as "Chlorodyne" or Dover's powder for exhausting diarrhœa, charcoal and kaolin for flatulence and liquid paraffin for constipation.

Recent work on the capacity of different micro-organisms in the gastro-intestinal tract both to produce and to compete for the use of, essential food factors indicates the desirability of early reinforcement of the factor or factors available for the body in insufficient quantity in sprue.

The high incidence of sprue or of sprue-like symptoms in British and Indian troops who were given prolonged courses of sulphonamides for dysentery has been ascribed by some to competition by the drug molecules for essential food factors. Similar developments in the course of prolonged oral administration of anti-biotics such as *chloromycetin* have strengthened that view.

The missing factors are present in liver extracts refined even to such a degree as is "Anahæmin." Crude extracts are generally cheaper but may be more painful on injection and are more liable to produce undesirable allergic effects.

Folic acid given by mouth in comparatively small doses rapidly

tropical areas with under 10 inches of rain a year (*see* Fig. 48). In Japan the disease is said to be less severe in the warmer than in the colder areas. On the other hand, J. Lowe in Calcutta found the greatest clinical and bacterial activity in the hot season.

Ætiology. The lepra bacillus is present in such enormous numbers in the nodular thickenings of the skin, and to a less extent in the thickened nerves, that it is universally accepted as the essential cause of the disease. Temporary nodules containing the organism have, moreover, been produced by several observers in monkeys by the direct inoculation of fresh tissues containing the lepra bacilli. More extensive lesions have been produced in the Syrian hamster, *Critelus auratus*, by

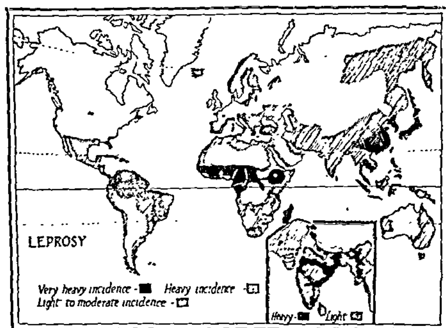


FIG. 48. Map of World incidence of leprosy.

injection of the rat-leprosy bacillus by Balfour-Jones in 1936 and with human leprous material by S. Adler and others later, but J. Lowe in Calcutta obtained only negative results in a number of these animals. The bacillus (*see* coloured plate, Fig. 66) is acid-fast, like its close relation the tubercle bacillus ; it occurs as a rod-shaped organism, which differs from that of tuberculosis in its presence in immense numbers arranged in bunches ; these form acid-fast masses in large " lepra cells " in the affected tissues of the deeper fibrous layers of the skin and in the fibrous sheaths of the affected nerves. The lepra bacilli are more easily decolorised by dilute acids, but less so by alcohol, than the tubercle bacilli. Moreover, the lepra bacilli cannot readily be cultivated like tubercle bacilli, nor do they produce tuberculosis when injected into guinea-pigs ; these tests are sufficient to show that the two bacilli are quite distinct from each other.

CHAPTER XVI

LEPROSY

Definition. Leprosy is a chronic disease caused by the acid-fast *Mycobacterium lepræ.* *The chief feature of the disease is the formation* of granulomata which occur chiefly in the skin and nerves and cause slowly developing deformities and trophic lesions. The onset is usually insidious. There are two chief types of the disease : (1) the lepromatous form, which attacks the skin and often ends in death after a prolonged illness ; (2) the neural type, including the tuberculoid form, in which the infection tends to die out, leaving in many cases permanent crippling of the hands and feet.

History and Spread over the World. The disease has probably been known in Africa, India and China, for several thousand years so the place of its origin is obscure. It appears to have spread from Asia into south-east Europe about 350 B.C., and it was recorded in Great Britain in the seventh century ; it increased in the middle ages during the time of the Crusades, but declined in the fourteenth century after the Black Death of 1349. While declining in Europe, it was carried to the Western Hemisphere from Spain and Portugal, and by the slave trade from Africa. During the second half of the nineteenth century leprosy was spread to Oceania by Chinese immigrants, where it caused several serious outbreaks ; human intercourse was thus the mode of spread. *The most important date in the history of leprosy* was the discovery of the lepra bacillus by Hansen in 1871.

Prevalence and Distribution. Estimates place the number of lepers in the world at three to five millions including a majority of early undetected cases. The largest numbers are found in India, China and tropical Africa, but much the highest rates per mille are found in the last-named, although the total number is probably not so great as in Asia on account of the sparseness of the population of most of Africa. There are some parts of tropical Africa where the proportion of obvious lepers is as high as five to twenty per mille, against the figure of 0·42 per mille in India, which is recorded in the census report of 1931. The latter is certainly too low an estimate, as E. Muir found four early cases for each advanced one in extensive surveys. In Europe indigenous cases still remain in Iceland, Norway, Sweden, the Baltic and Balkan provinces, Crete, Spain, Portugal, Italy and a very few in the Maritime Alps. An inquiry in 1939 indicated that there were under fifty cases in Great Britain, none of which were indigenous, and that nearly all the infective lepromatous cases were under skilled medical control. There was some increase of cases after the world wars of 1914–18 and 1939–45. A map of the world incidence shows high ratios in humid tropical areas with high rainfall, and little or none in the few dry

Culion, in the Philippines, where 5,000 lepers live under ordinary family conditions, that inherited leprosy does not occur. Moreover, in India hundreds of children who have been separated from their leper parents at birth have remained healthy to the second generation, so that we may safely discard the paralysing theory of hereditary transmission.

Age Incidence. Children are far more susceptible to leprosy than adults, but those under five years of age are less frequently found affected owing to the fact that the incubation period averages between two and three years. Thus, in the data of some 4,000 cases collected by L. Rogers, in which the age of onset was recorded and allowance was made for the incubation period, it was found that about 50 per cent. had been infected before the age of twenty years, two-thirds before twenty-five, and three-fourths by the age of thirty, after which susceptibility steadily declines, although no age is entirely exempt. The disease is very liable to appear about the age of puberty. In Norway among 2,010 children of 587 couples recorded by Sand and Lie, where the father alone was a leper, 7 per cent. contracted the disease ; where the mother was a leper, 14 per cent. ; and when both parents were lepers, 26 per cent. of the children were infected. The proportion of infections obviously depends on the closeness of contact with the infected persons. In the earlier days of the great Culion leper settlement, when the conditions did not allow of the separation of newly-born children from their leper parents on account of the high attendant mortality, no less than 36 to 44 per cent. of children living with their infected parents up to about ten years of age contracted the disease. Later Rodriguez reported that of children separated from their leper parents at from six months to eleven years of age, 28 per cent. developed the disease during the next four years, and a still later account states that 10–15 per cent. of the children separated from their leper mothers at the age of six months were subsequently found to have been infected within that period. Recently, with the better conditions now obtaining it has been found possible to take away the children at birth from their mothers, greatly to their benefit. The comparative infrequency of infection under conjugal conditions, namely, in only 3–5 per cent. of persons exposed to such contact, is due to the lower susceptibility of adults.

Sex Incidence. After childhood males more frequently contract leprosy than females ; this appears to be due to the greater extent to which they come into contact with other persons in their occupations and amusements. In this connection it is of interest to note that in the Galicia province of Spain more females were said to be lepers owing to their living promiscuously during long absences of their husbands.

The Infectivity of Leprosy and the Favouring Conditions. The conditions under which leprosy infection takes place are well-illustrated in a table in *Leprosy* of 700 cases in which the probable source of

Many workers have claimed to have cultivated the lepra bacillus by various methods, but there are great discrepancies not only in the methods employed, but also in the descriptions of the organisms obtained, and authorities agree that no satisfactory proof of successful cultivation has yet been furnished. It is likely that the saprophytic acid-fast organisms, so common on the skin of healthy persons, have often been mistaken for the lepra bacilli. In 1932 Soule and McKinley reported growing the *Mycobacterium lepræ* in cultures of human and chick embryonic tissues suspended in Tyrode's solution up to sixteen generations in the course of eighteen months, preferably in 40 per cent. O_2 and 10 per cent. CO_2, but after the ninth transfer the organisms failed to infect monkeys, although the inoculation of fresh leprous material did so. Salle and Mosir claim to have confirmed this work, but J. Lowe failed to do so in Calcutta. In 1939 McKinley himself published a comprehensive review of the bacteriology of leprosy; he concluded that although there can be no good reason to doubt the relation of Hansen's bacillus to leprosy, none of the organisms yet cultivated has been proved to be the cause of the disease.

Rat leprosy is a skin disease of these rodents closely resembling the dermal form of leprosy and caused by an acid-fast bacillus. E. Marchoux, in Paris, showed that the disease is readily inoculable into other rats by means of fresh material from infected animals; this material can maintain its activity if kept in a moist state for several months; it produces a generalised infection with granulomata in the spleen and liver. The acid-fast bacillus of rat leprosy has not yet been cultivated. However, the infection of male rats by Marchoux and Sorel and of females by Clorine and Berny through the local application of rat-leprosy material to the genital organs, suggests the possibility of direct infection by sexual intercourse in the rare cases of leprotic lesions in those situations. Marchoux and Clorine in 1938 also reported the infection of rodents with rat-leprosy bacilli through the rectal and oral mucous membranes and through the conjunctiva. The smallest superficial lesion or abrasions, or even pulling out hairs by their roots, allow of penetration of the skin by the rat-leprosy, or Stefansky's bacillus. Moreover, white rats can be infected with certainty by the inoculation of only five bacilli.

Heredity was accepted in Western Europe in the middle of the nineteenth century as the chief factor in the causation of the disease, but this view was based chiefly on scanty Scandinavian evidence, which fails to stand the test of critical examination in the light of our present knowledge of heredity and of leprosy. The chief fallacy was that no account was taken of the part played by close personal contact in spreading the disease. This is now known to be the most important factor of all, and the close association between members of a family gives ample opportunities for contact to occur.

There is abundant evidence from the great leper settlement of

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Sex Incidence. After childhood males more frequently contract leprosy than females ; this appears to be due to the greater extent to which they come into contact with other persons in their occupations and amusements. In this connection it is of interest to note that in the Galicia province of Spain more females were said to be lepers owing to their living promiscuously during long absences of their husbands.

The Infectivity of Leprosy and the Favouring Conditions. The conditions under which leprosy infection takes place are well-illustrated in a table in *Leprosy* of 700 cases in which the probable source of

Many workers have claimed to have cultivated the lepra bacillus by various methods, but there are great discrepancies not only in the methods employed, but also in the descriptions of the organisms obtained, and authorities agree that no satisfactory proof of successful cultivation has yet been furnished. It is likely that the saprophytic acid-fast organisms, so common on the skin of healthy persons, have often been mistaken for the lepra bacilli. In 1932 Soule and McKinley reported growing the *Mycobacterium lepræ* in cultures of human and chick embryonic tissues suspended in Tyrode's solution up to sixteen generations in the course of eighteen months, preferably in 40 per cent. O_2 and 10 per cent. CO_2, but after the ninth transfer the organisms failed to infect monkeys, although the inoculation of fresh leprous material did so. Salle and Mosir claim to have confirmed this work, but J. Lowe failed to do so in Calcutta. In 1939 McKinley himself published a comprehensive review of the bacteriology of leprosy; he concluded that although there can be no good reason to doubt the relation of Hansen's bacillus to leprosy, none of the organisms yet cultivated has been proved to be the cause of the disease.

Rat leprosy is a skin disease of these rodents closely resembling the dermal form of leprosy and caused by an acid-fast bacillus. E. Marchoux, in Paris, showed that the disease is readily inoculable into other rats by means of fresh material from infected animals; this material can maintain its activity if kept in a moist state for several months; it produces a generalised infection with granulomata in the spleen and liver. The acid-fast bacillus of rat leprosy has not yet been cultivated. However, the infection of male rats by Marchoux and Sorel and of females by Clorine and Berny through the local application of rat-leprosy material to the genital organs, suggests the possibility of direct infection by sexual intercourse in the rare cases of leprotic lesions in those situations. Marchoux and Clorine in 1938 also reported the infection of rodents with rat-leprosy bacilli through the rectal and oral mucous membranes and through the conjunctiva. The smallest superficial lesion or abrasions, or even pulling out hairs by their roots, allow of penetration of the skin by the rat-leprosy, or Stefansky's bacillus. Moreover, white rats can be infected with certainty by the inoculation of only five bacilli.

Heredity was accepted in Western Europe in the middle of the nineteenth century as the chief factor in the causation of the disease, but this view was based chiefly on scanty Scandinavian evidence, which fails to stand the test of critical examination in the light of our present knowledge of heredity and of leprosy. The chief fallacy was that no account was taken of the part played by close personal contact in spreading the disease. This is now known to be the most important factor of all, and the close association between members of a family gives ample opportunities for contact to occur.

There is abundant evidence from the great leper sett[illegible] of

the nerve form, for among 113 cases in which the type of the infecting leper was recorded 95 per cent. were of the nodular and only 5 per cent. were nerve cases. The latter were probably mixed nerve and lepromatous cases, for Dharmendra and Sen found that of 2,820 nerve cases

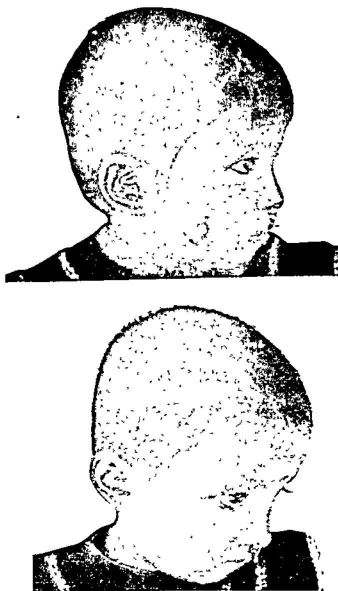


FIG. 49. Probable initial lesion on face of child infected by lying on pillow soiled with lepra bacilli, and scar left after eight months' treatment. (Rogers and Muir's *Leprosy*.)

with negative skin smears only 0·17 per cent. gave positive nasal smears, but of 447 nerve cases with positive skin smears nasal infections were found in 35·4 per cent.

Probable Mode of Infection. The actual mode of infection is not yet known with certainty, but it is highly probable that the lepra

infection was traced and classified in round numbers, thus : in one-fifth infection was traced to sexual relationship with a leper ; in two-fifths to living in the same house with a leper (one-fourth of these had slept in the same bed with a leper) ; in one-fifth to personal attendance on a leper, usually while living in the same house ; and the remaining one-fifth to close association with a leper. Thus, approximately 80 per cent. of the infections were contracted while living in the same house with a leper ; 30 per cent. of them had actually slept in the same bed with a subject of the disease. Nevertheless, only 3-5 per cent. of all the persons who live in the same house with a leper contract the disease, so that leprosy is by no means a highly contagious disease ; it is, in fact, not so infectious as tuberculosis, and it is only the terror associated with the deformities produced by leprosy which has caused the long-standing belief in its great infectivity. At Cebu in the Philippines a close relationship has been demonstrated between density of population and leprosy prevalence, and in India Muir has found high incidence among crowded labour forces composed of primitive aboriginal people in contact with civilisation ; he believes that markets and pilgrimages may be factors in spreading the disease.

In a very few cases leprosy is reported to have been communicated through arm-to-arm vaccination, which is not now practised. Two boys are known to have been infected by accidental inoculation from leper playmates, and three doctors through wounds received while operating on lepers. In all of these the disease commenced in the wounded finger. Even more conclusive is the case of two sailors tattooed at the same time, who both developed the first signs of leprosy at the sites of the tattoo marks. It is thus clear that the disease is inoculable, although, with one doubtful exception, it has not been artificially communicated to volunteers in this way, in spite of a number of trials, but they were nearly all made in slightly susceptible persons over thirty years of age ; this probably accounts for the failures. Still more conclusive is the instance of the heroic Egyptian doctor, who on three occasions inoculated himself intravenously with fresh material containing innumerable lepra bacilli ; with the result that only forty days later small lepromata appeared on his skin and unfortunately he died of leprosy several years later. *Insect bites* have been suspected as a possible cause, but much experimental work has failed to confirm this hypothesis. In Africa, Moiser found acid-fast bacilli in cockroaches, which he suggested might be sources of leprosy infection in man. As the organisms could be cultivated readily it is most unlikely that they were lepra bacilli. Persons who have worn lepers' clothing have contracted the disease on several occasions, and wet-nurses have infected children whom they suckled. Bad fish may predispose to leprosy, as shown by E. Muir in India, but is not the direct cause of infection, as once suggested.

Lepromatous or Nodular leprosy is twenty times more infective than

a-half months, and in 81 per cent. of the cases the period was less than five years; an important point from the prophylactic side as will appear later. The rare cases in which the disease has been discovered many years after the patient has left a leprous country can generally be explained by the early stages having been overlooked; it is only when some failure of health causes an easily recognised exacerbation



Fig. 50. Early erythematous leprosy eruption on back. (Rogers and Muir's *Leprosy*.)

that the disease is discovered. The closer the contact the shorter the incubation period, due to more intense infection.

Primary Lesions. Although there is no definite primary lesion in leprosy comparable to that of syphilis, in places where many early leprosy cases are seen (in the absence of compulsory segregation causing them to be hidden), a well-marked single lesion is often found, which is probably the site of the inoculation of the disease. For instance, E. Muir described a patch on the face of a child who had lain on the soiled bedding of a leprous parent (*see* Fig. 49). At a Philippine skin

bacilli escaping from the lesions of advanced cases of the disease enter the skin of persons who come into close contact with infective persons. Abrasions and the punctures of insect bites are probable avenues of infection. The bacilli are found in the nasal mucous secretions in from 70–90 per cent. of advanced nodular lepers. E. Muir found them in the nasal mucus of 37 per cent. of earlier skin and mixed cases in Calcutta, but in only 3·8 per cent. of nerve cases; another illustration of the far greater infectivity of the former types. Ulcerating nodules discharge immense numbers of the organisms, but the trophic ulcers of nerve cases are usually free from them.

The distribution of the first noticed lesions of leprosy in over 1,000 Indian cases reported on by E. Muir throws further light on the subject. They were nearly all found on the exposed extensor surfaces of extremities, on the face, and on parts exposed to pressure, such as the buttocks, through which infection may occur by lying on a bed soiled with discharges from a leper's nose or sores (*see* Fig. 49), but rarely on parts which are covered by the clothes and free from pressure. The soft, moist skin in hot, humid climates, and the number of minute lesions in the exposed parts of the skin caused by insect bites, would favour the entry of the bacilli, and so account for the high incidence in such climates. All the evidence thus points to infection through the skin of persons in close contact with lepers, and, although it is not possible absolutely to exclude infection by ingestion, there appears to be no definite evidence of its occurrence. Infection is also possible directly through sexual intercourse, but the recorded cases of men developing the disease within a few months of an intercourse with a leper woman on a single occasion can easily be explained by infection through the skin owing to the close bodily contact involved. The frequency of infection of young children is readily accounted for on the same hypothesis; also the high incidence of the disease among backward and poor tribes among whom overcrowding, close personal contact and lack of cleanliness prevail. Infection of those working in leprosy institutions has been extremely rare and has usually been due to carelessness.

CLINICAL DESCRIPTION

Nothing is easier than to recognise at a glance an incurable advanced case of leprosy; few things in medicine require more experience than to detect the earliest cases, and, as these are the more important because they are usually amenable to treatment, they must be described in greater detail.

The incubation period is not usually so long as used to be thought, for Culion data show that the incubation averaged three and a half years in the children who had been isolated from their leprous parents at different times, and who subsequently developed leprosy. In eighty-four cases collected by L. Rogers it averaged two years and eight-and-

the nasal mucosa was never found to be infected before the skin ; in many the skin alone showed signs of the disease.

Classification. Leprosy cases have long been divided into (1) Cutaneous or Lepromatous ; (2) Neural ; and (3) Mixed, in accordance with the tissues mainly affected. In 1947 the Brazil Leprosy Conference adopted the following classification :—

1. **Uncharacteristic or Unidentified.** Macular, neural and generalised (U I), the histology of which shows only simple round-celled infiltration.

2. **Tuberculoid** (T). Macular, papular, neural and reactive with tuberculoid changes microscopically.



FIG. 52. Nodular or lepromatous leprosy before and after treatment. (Muir, *Proc. Roy. Soc. Med.*)

3. **Lepromatous** (L). Macular, infiltrative, nodular and generalised, which show very numerous lepra bacilli often in bundles in large degenerating cells of the foamy type.

This classification requires microscopical examinations when practicable. The uncharacteristic type may develop into either tuberculoid or lepromatous cases. Most authorities hold that tuberculoid cases very rarely become lepromatous ; a few think this evolution may be more frequent.

Lesions in Lepromatous or Cutaneous Cases. In the earliest skin lesions infiltration of the papillary layer of the corium produces smooth erythematous patches, and next the bacilli cause thickening of the

clinic Rodriguez found a single initial lesion in 93 per cent. of early cases. An analysis of 252 such cases in a single institution in India showed that in 75 per cent. the first lesion was a depigmented anæsthetic patch ; in 10 per cent. there were depigmented non-anæsthetic ones, in 12 per cent. erythematous red patches, in 2 per cent. erythematous

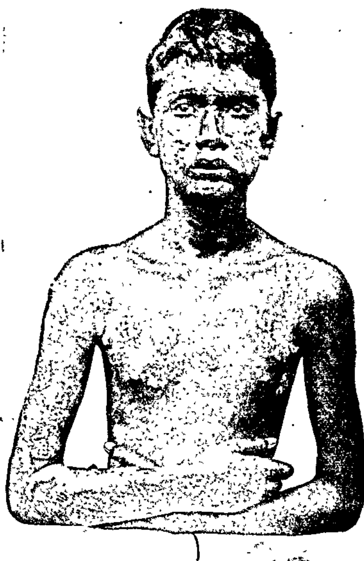


Fig. 51. Major tuberculoid lesions during severe reaction. (Rogers and Muir's *Leprosy*.)

anæsthetic patches, in 1·5 per cent. ulcers, and in 5 per cent. there was paralysis due to nerve involvement. In the Philippines Chiyuto reported very similar observations.

The primary infection thus appears to occur in the skin. The view once held that the nasal mucous membrane is a common site of infection has not been supported by recent work, for among the several hundred children of lepers carefully examined for the first symptoms at Culion,

perforating ulcers and necrosis of bones ; these require surgical treatment, and healing takes place readily after operations for the removal of necrosed fragments. Much shortening of digits may result from bone atrophy, with preservation of the nails and without any actual ulceration. In an earlier stage blisters may appear on anæsthetic areas, especially of the fingers.

Tuberculoid leprosy is met with mainly in Northern India and parts of Africa, and has been minutely studied by H. W. Wade. It is characterised by localised dermal lesions, commonly associated with thickening of the nerves supplying the affected areas which are round or oval patches, with thickened reddish edges and central paler anæsthetic areas. Microscopically they show extensive granulomatous and epithelioid infiltration and a few giant cells, but extremely few lepra bacilli, which may be difficult to detect. This differentiates them from lepromatous skin lesions with very numerous bacilli ; a very important distinction, because the occurrence of tuberculoid lesions indicates a high degree of resistance to the invading organisms, and the lesions are of a mild type amenable to treatment, in contrast with the progressive lepromatous type. Areas with much thickened, elevated, and clearly defined, margins are classed as major to distinguish them from earlier less easily recognised minor forms.

Reactions in Leprosy. These are important and occur, as a rule, either in the natural course of progressive cases or following treatment, usually of too vigorous a nature. They consist of a sudden swelling and softening of existing lesions, often with the appearance of new ones in the skin, usually accompanied by fever of either short or, more rarely, of long duration, with increasing weakness of the patient. In neural cases swelling up of a thickened nerve with severe pain in its distribution occurs. Reactions are followed in a short time by subsidence of the inflammatory changes in the leprous lesions, sometimes with great general improvement. As an exacerbation in the form of a reaction often first brings the patient under medical treatment, it is important to avoid the error of attributing the subsidence of the reaction to the effects of any given treatment. When prolonged febrile reactions ensue on active treatment they are liable to be harmful by lowering the resistance of the patient, but they may ocasionally be followed by remarkable improvement over a long period.

Mucous Membranes. That of the nose is involved in dermal leprosy, and this leads to the discharge of blood-stained mucus, containing large numbers of lepra bacilli which constitute the greatest danger of infection to contacts, so that all handkerchiefs should be disinfected. The bacilli can often be found in smears obtained by swabbing the nasal mucosa, and all patients who are positive should be regarded as infectious. Swelling of the mucous membrane may interfere with breathing through the nose, and ulceration may occur especially on the anterior portion of the septum. The disease may

tissues between the hair follicles, producing an exaggeration of the natural folds of the skin, the surface of which has a mosaic-like appearance ; later still the infiltration spreads deeper than the follicles and causes a general smooth thickening of the skin in patches. These in time may go on to the formation of actual nodules, in which there are swarms of the acid-fast rod-shaped lepra bacilli, which tend to group themselves in the characteristic intracellular bundles. In addition to being found in large lepra cells the bacilli often invade the lymphatic channels, and spread through them to the deeper skin layers.

In the neural type the terminal nerve fibres in the skin may first be involved, with a tendency to spread up the small nerves ; the lepra bacilli are very scanty and difficult to find in the affected skin. In this way depigmented light-coloured anæsthetic patches are produced, often with anhidrosis, or hyperæsthesia to light touch may exist for a short time before the onset of the loss of sensation. Parakeratosis and hyperkeratosis, producing a shiny, smooth, scaly appearance, is often seen over the skin, or on the palms of the hands and soles of the feet ; the hairs tend to become thick and break off, and the nails show trophic changes. This form often begins as a single white depigmented anæsthetic patch, which may become surrounded with a raised erythematous ring in which scanty lepra bacilli may be found, although they are absent from the anæsthetic pale central area. This is probably the site of primary infection ; the disease spreads up the terminal sensory nerve fibres, and hence is called by E. Muir the ascending type, as opposed to the metastatic sub-type, in which the infection reaches the nerve trunks through the blood stream and spreads through the connective tissue of the nerves by the lymphatic channels, to produce great thickening, often of an irregular nodular nature, and containing many lepra bacilli ; there may even be abscesses within the nerve sheath.

The most frequently affected nerve trunks are the ulnars at the bend of the elbow, the external peroneals as they wind round the upper end of the fibula, the great auriculars in the neck, the radials and the supraorbitals, but great thickening of superficial nerves may be met with in other parts of the body, sometimes leading to a macular thickened patch on the skin.

The most common type is the ulnar, in which there is great thickening of one or both nerves just above the elbow joint, with accompanying loss of sensation in the ulnar side of the hand and forearm, also weakness and contractures of the ring and little fingers. In advanced cases the radial nerves also frequently become involved, with eventual atrophy of many of the intrinsic muscles of the hand and the characteristic claw-hand deformity and contractures resulting from this. There may be loss of digits due to injuries which are not noticed owing to the loss of sensation. Thinning and partial absorption of the digital bones may be detected by X-rays, and similar lesions occur in the feet, often with

for examination on account of more extensive anæsthesia of an extremity, thickening of the ulnar or peroneal nerves should be sought for, and if the patient has been in a leprous area and no other cause of neuritis is present, treatment should be commenced, even if the nasal mucus is free from acid-fast bacilli, as will usually be the case. In late nerve cases with mutilation bacteriological examinations will usually also be negative, but treatment in these advanced cases can do little for the unfortunate victim.

In the earliest dermal lesions, again, a clinical diagnosis can usually be made before microscopical examinations of the skin or nasal mucus yield acid-fast bacilli. The characteristic features are erythematous patches, which are most commonly situated on the back and show no definite loss of sensation, although small areas may reveal this important corroborative sign, and the nasal mucus is more frequently positive than in early nerve cases. More frequently there is some thickening of the first dermal patch, or when a number of lesions have appeared within a short time one or more of these may be thickened.

Microscopical Examination. By cutting out a small piece of such a thickened area, including the deeper connective tissue layers of the skin, with a pair of scissors curved on the flat, and smearing the under surface of the excised portion on a clean slide, a preparation is obtained which shows numerous characteristic bacilli, with appropriate staining by the carbol fuchsin method, in lepromatous cases, but very few or none in tuberculoid lesions. The presence of the bacilli puts the diagnosis beyond doubt. Anæsthetic areas should be avoided in carrying out this examination, as they contain few or no lepra bacilli. A thickened lobule of the ear is convenient for examination, as it is not very sensitive. In many dermal cases abundant lepra bacilli can be found in unthickened ear lobes, and also sometimes in the apparently healthy skin of other parts of the body (masked leprosy). Muir has demonstrated acid-fast bacilli in light scrapings of the superficial cornefied epithelium in dermal cases ; this suggests that the bacilli may escape from the body in the absence of ulceration.

To stain the bacilli, drop carbol fuchsin stain on a dried film, heat until steam rises, then let the slide cool, and leave the stain on for ten to thirty minutes ; wash and decolorise with 10 per cent. hydrochloric or sulphuric acid in alcohol for one or two minutes, wash again and counter-stain with methylene blue for two minutes, and examine under an oil-immersion lens. The presence of numerous red granules indicates degeneration and breaking up of the bacilli ; the prognosis is better when these red-stained granules are numerous.

The bacilli are rarely found in the nose if they are not present in the skin. The examination is made by holding a pledget of sterile cottonwool in a pair of forceps and rubbing it over any congested or thickened patch in the anterior portion of the nostril ; the mucus is then smeared on a slide for staining and examination.

spread to the pharynx and the mouth, and produce nodular thickening or ulceration. If this condition involves the larynx it becomes highly dangerous, as any reaction may produce swelling of the thickened tissues and cause suffocation or necessitate tracheotomy, but fortunately this is not common. The sputum may rarely show numerous acid-fast lepra bacilli, which are not cultivable.

Eye lesions sometimes occur, they include ulceration of the cornea followed by opacity, or thickening of the iris and neighbouring parts constituting iridocyclitis ; this may go on to loss of sight. All eye lesions greatly handicap treatment, as there is a danger of injurious reactions, such as destruction of the delicate tissues inside the eye following chaulmoogra treatment. Paralysis of the sensory nerves or paralysis of the orbicular muscles may also expose the eye to injury.

The internal organs may be found affected and sometimes contain ✓ lepra bacilli. The liver is not uncommonly involved. Muir now *considers that bacilli in the sputum originate from nodules in the* trachea and bronchi, and not from the lung tissues.

Lymph glands may be enlarged and contain lepra bacilli, and work in Culion has shown that puncture of the superficial glands may enable the bacilli to be found when the skin has become negative.

The testicles are involved in most of the advanced cases, and sterility is often caused in this way. **The ovaries** are affected much less frequently, and most leper women retain their fertility ; Lampe, in Surinam, found the fertility rate to be 6·3 in healthy and 7·8 in leprous women. Mental depression may occur as an indirect effect of leprosy.

Diagnosis. Advanced lepromatous (except in masked cases (*see* p. 325)) and nerve cases of leprosy can be recognised at a glance, but most of these advanced cases cannot be expected to benefit greatly by treatment. The diagnosis in the earliest and most amenable stage is sometimes difficult for those who have not had considerable clinical experience of the disease. To get the best results from the improved *modern form of treatment it is essential to recognise* the early lesions, even when they are still negative to bacteriological examination. As already mentioned, three-fourths of the primary lesions consist of depigmented, or occasionally of erythematous anæsthetic patches, which may be found on almost any part of the body, so that in examining " contacts " for early symptoms of the disease the patients should be stripped as far as possible. Any light-coloured depigmented areas should be examined carefully for loss of sensation to light touch by means of a piece of cotton wool or rolled-up paper. Thickening of any neighbouring superficial nerve should be looked for. In this stage bacteriological examination *is nearly always negative*, though bacilli may sometimes be found in the surrounding zone of erythematous skin. The nasal mucus is almost certain to be free from lepra bacilli, so the diagnosis *must* be made on clinical grounds, and treatment should be started at once with a good prospect of success. In patients who come

is no thickening of the superficial nerves. Dermal leishmaniasis may resemble nodular leprosy, but is easily distinguished if the Leishmania bodies are sought for (*see* Fig. 66 of coloured plate).

Diagnosis in Young Children. The usual initial lesion is a macule which may contain the bacilli, but the nasal mucosa does not usually show bacilli before the age of nine. In the Philippines C. B. Lara found the earliest signs in children were on the arms, legs and buttocks which most frequently come into contact with infected parents.

Prognosis. This depends on the stage of the disease and always requires great caution. Advanced mutilated nerve cases are obviously beyond remedy, but the infectivity tends to die out and the patients may live for several decades until released by some intercurrent disease. In advanced nodular cases, in the absence of the modern treatment, death usually takes place in eight to ten years, and in the acute febrile type in two or three years. The outlook for lepromatous cases has been greatly improved by the introduction of the sulphone treatment. In areas where a large proportion of the cases are of the resistant nodular type, the prognosis is much worse than where mild nerve and tuberculoid cases preponderate. In Malaya G. A. Ryrie found plantar hyperalgesia on stroking the sole of the foot with a hard instrument, an early and unfavourable sign in lepromatous cases. At the Deccan Dichpali Leper Hospital, to which only comparatively early and hopeful cases are admitted, about 90 per cent. are discharged recovered after about eighteen months' to two years' treatment, and such relapses as occur usually clear up again on further treatment. At the commencement of treatment a very guarded prognosis should be given, especially in cases with rapid appearance of widespread lesions, and still more if successive crops are accompanied by febrile attacks ; such cases tend to run a rapid course and may not prove amenable to any treatment. All cases should be kept under observation at frequent intervals for two to four years after the disappearance of all active symptoms, so that treatment can be resumed at once on the occurrence of the slightest relapse. Very early nerve cases may not infrequently recover spontaneously without treatment.

A positive lepromin test indicates good resisting powers with a corresponding favourable prognosis, a negative one has the opposite significance.

TREATMENT

History. Of the many remedies recommended during the nineteenth century for the treatment of leprosy the chaulmoogra oils and their derivatives alone remain in common use. In India for a thousand years they were obtained from the ripe seeds of *Taraktogenus kurzii* of Burma and *Hydnocarpus wightiana* of the Western Ghat mountains, but were too nauseating to be taken in sufficient quantities to do more than slightly retard the progress of the advanced cases of leprosy

The Lepromin or Mitsuda test is performed by the intradermal injection, or the application to the scarified skin of a sterile emulsion of a leprous nodule containing very numerous lepra bacilli. In positive cases this is followed in twenty-four hours by an erythematous halo, followed by a more characteristic late reaction seven to ten days later and reaching its maximum in three or four weeks, in the form of induration with a diameter of 4 or 5 mm. up to 20 mm. often ending in ulceration and persisting for several weeks. Dharmendra in Calcutta has shown that if the lepra bacilli are separated from the tissue of the nodules by repeated centrifugation and then ground to break them up before making the injection, the early fourteen-hour reaction is greatly increased in degree and the late one correspondingly reduced. Further experiment showed that it is the protein fraction of the bacilli that is active and this modification does away with both the long delay in reading the result and in the undesirable late ulceration.

The reaction appears to be an allergic one and is of great prognostic, but not of diagnostic, value, for negative results are obtained in about 90 per cent. of the resistant lepromatous cases, and only weakly positive ones in the remaining 10 per cent. On the other hand, neural cases give only 6–22 per cent. of negative reactions and nearly all tuberculoid cases give positive reactions. There is also evidence that the prognosis is better in lepromatous cases giving slightly positive reactions and worse in neural cases showing negative reactions.

The Histamine Test. Argentine workers have reported that on lightly pricking the skin of anæsthetic leprosy patches through a drop of 1 in 1,000 solution of phosphate of histamine in double distilled water local congestion appears within about half an hour, an erythematous areola in about two hours, and an œdematous papule a little later. The healthy skin of both controls and of leprosy patients give negative results, so this reaction is of diagnostic value in neural cases.

The Rubino reaction consists in the rapid agglutination and sedimentation of sheep's red corpuscles by the serum of leprosy cases in 71 per cent. of lepromatous, 33 per cent. of nerve and in 20 per cent. of maculo-anæsthetic ones, according to E. Rudolf. As only 1 per cent. of a large number of control cases reacted, it is of diagnostic importance.

Differential Diagnosis. The conditions most likely to be confused with leprosy are : (1) syphilis, which gives a positive Kahn reaction, while uncomplicated leprosy is negative ; (2) leucoderma, the patches of which are not anæsthetic, while they are usually much more extensive and symmetrical than those of early nerve leprosy, with which they are liable to be confused ; (3) tinea, recognised by the presence of the fungus ; (4) psoriasis, which has no acid-fast bacilli or anæsthesia, and (5) tuberculosis and lupus erythematosus.

The nerve form may be simulated by syringomyelia, in which there

or of the thickened nerves; when this happens, wait for a week or more until the reaction has completely subsided and reduce the next dose by 0·5 c.c.; increase again as before, and, as a rule, no further reaction will occur. To obtain the best results the dose should be pushed as far as possible short of producing prolonged injurious reactions. Thus Ryrie advises 1 c.c. of hydnocarpus oil per 10 lb. body weight up to 30 c.c. a week as a minimum and at least 50 per cent. more in acute cases, when improvement may be expected within three months. With such large doses he noted much more marked improvement and a much lower incidence of lepromatous changes.

The ethyl esters of the whole oils are rather more painful on injection, but the pain is reduced by adding 1 per cent. iodine as used at Culion. With the pure ethyl esters the maximum doses which are well borne vary from 3 to 5 c.c. They are also given intradermally. Here again the dosage must be pushed, for Schujman recorded that all his cases which became bacteriologically negative had been given a total dosage of 1,500 c.c. intramuscularly and intradermally and 40 per cent. of the lepromatous cases had become clinically and bacteriologically negative.

Sodium hydnocarpate is best given intramuscularly. The dosage should be rapidly increased from 0·5 to 7 or even 10 c.c. of a 3 per cent. solution once or twice a week. Solutions made up to the normal *p*H are nearly painless. If improvement ceases Rogers advises the intravenous injection of 1–2 per cent. solutions intravenously for a time to the point of producing slight reactions, following which he observed more rapid improvement, but most observers prefer to avoid all reactions and this is imperative in all patients showing involvement of the eyes. Sclerosis of the veins can be avoided by Muir's plan of drawing up an equal quantity of blood into the syringe containing the solution and then slowly injecting the whole.

Results of Chaulmoogrates Parenterally. These depend on the type and stage of the disease. No drug can remove the disabilities of old crippled nerve cases, but early neural and tuberculoid patients readily respond, as do most early lepromatous ones. Muir in 1927, as the result of treating several thousand cases during seven years, reported that in early cases the permanent disappearance of all active signs of the disease indicates that for all practical purposes the patients are cured. In the Bombay Deccan Isabel Kerr recorded that when only early cases most suitable for treatment were admitted anything up to 90 per cent. were discharged recovered after one or two years; a small percentage relapsed, but responded to further treatment. On the other hand, in advanced cases at the Philippines Culion settlement Wade and Gara reported that several years' treatment resulted in apparent cures in only 15–20 per cent. On the other hand, Schujman in South America in 1948, with 20–30 c.c. chaulmoogra oil weekly for two years, reported as good results as with promin and claimed 40 per cent. of

which formed a very high percentage of admissions to the prison-like asylums of India and elsewhere.

In 1854 Mouart of Madras introduced chaulmoogra oils to European medicine and in 1879 Moss separated out the lower melting point fatty acids under the name of "gynocardic acid." In 1904–07 Power of the Wellcome Chemical Laboratory showed that Moss's preparation consisted mainly of hydnocarpic acid with a melting point of 49° C., which with chaulmoogric acid with a melting point of 68° C., form the essential part of the oils. In 1916 Ralph Hopkins with fifteen years' experience recorded that some incipient cases had cleared up under prolonged treatment with the oil.

In 1914 Heiser in the Philippines reported clearing up of the symptoms in some advanced cases by intragluteal injections of chaulmoogra oils, but a later report by Wade showed that they relapsed. In the meantime by 1912 Rogers in Calcutta in early cases had obtained improved results with clearing up of extensive cutaneous lesions in a medical man, by the oral use of large doses of gynocardic acid. This led him to seek for a soluble product suitable for injection and in 1915 he obtained sodium gynocardate or hydnocarpate and gave it subcutaneously, intramuscularly and intravenously mostly in early cases obtained from a hospital out-patient department. He recorded his earlier work and preliminary trial of the new preparation in 1916 and in the following year reported that in cases of up to three years' duration 50 per cent. had been cleared of their symptoms and lepra bacilli, but in cases of longer duration only 25 per cent. had been cleared up. By 1920 41 per cent. of 51 cases had been cleared up and only one very advanced case had failed to show any improvement. On the other hand, none of the advanced cases treated somewhat irregularly in the local leper asylum had shown more than improvement. It thus became evident that cases must be treated fairly early to obtain full relief.

Confirmation by Muir and others in India was soon forthcoming and in 1919 Dean and Hollman in Hawaii reported equally good results from the injections of ethyl ester chaulmoogrates. A little later Muir used the much less costly fresh *Hydnocarpus wightiana* oil intramuscularly with the addition of 4 per cent. creosote and the Wellcome Laboratories made very cheap and convenient sodium salt of the more active lower-melting-point fatty acids of *H. wightiana* oil, and also an ethyl ester under the name of moogrol.

Dosage. The creosoted hydnocarpus oils are injected both intramuscularly and by the infiltration method into the skin lesions, the first dose being 0·5 c.c., and, as long as no febrile or local reaction occurs, it may be increased by 0·5 c.c. at each dose up to from 5 to 10 c.c., and given once or twice a week. The oil should be warmed before use to make it less viscid. A reaction may occur in the form of a rise of temperature or swelling up and redness with softening of the nodules

or of the thickened nerves ; when this happens, wait for a week or more until the reaction has completely subsided and reduce the next dose by 0·5 c.c. ; increase again as before, and, as a rule, no further reaction will occur. To obtain the best results the dose should be pushed as far as possible short of producing prolonged injurious reactions. Thus Ryrie advises 1 c.c. of hydnocarpus oil per 10 lb. body weight up to 30 c.c. a week as a minimum and at least 50 per cent. more in acute cases, when improvement may be expected within three months. With such large doses he noted much more marked improvement and a much lower incidence of lepromatous changes.

The ethyl esters of the whole oils are rather more painful on injection, but the pain is reduced by adding 1 per cent. iodine as used at Culion. With the pure ethyl esters the maximum doses which are well borne vary from 3 to 5 c.c. *They are also given intradermally.* Here again the dosage must be pushed, for Schujman recorded that all his cases which became bacteriologically negative had been given a total dosage of 1,500 c.c. intramuscularly and intradermally and 40 per cent. of the lepromatous cases had become clinically and bacteriologically negative.

Sodium hydnocarpate is best given intramuscularly. The dosage should be rapidly increased from 0·5 to 7 or even 10 c.c. of a 3 per cent. solution once or twice a week. Solutions made up to the normal *p*H are nearly painless. If improvement ceases Rogers advises the intravenous injection of 1–2 per cent. solutions intravenously for a time to the point of producing slight reactions, following which he observed more rapid improvement, but most observers prefer to avoid all reactions and this is imperative in all patients showing involvement of the eyes. Sclerosis of the veins can be avoided by Muir's plan of drawing up an equal quantity of blood into the syringe containing the solution and then slowly injecting the whole.

Results of Chaulmoogratės Parenterally. These depend on the type and stage of the disease. No drug can remove the disabilities of old crippled nerve cases, but early neural and tuberculoid patients readily respond, as do most early lepromatous ones. Muir in 1927, as the result of treating several thousand cases during seven years, reported that in early cases the permanent disappearance of all active signs of the disease indicates that for all practical purposes the patients are cured. In the Bombay Deccan Isabel Kerr recorded that when only early cases most suitable for treatment were admitted anything up to 90 per cent. were discharged recovered after one or two years ; a small percentage relapsed, but responded to further treatment. On the other hand, in advanced cases at the Philippines Culion settlement Wade and Gara reported that several years' treatment resulted in apparent cures in only 15–20 per cent. On the other hand, Schujman in South America in 1948, with 20–30 c.c. chaulmoogra oil weekly for two years, reported as good results as with promin and claimed 40 per cent. of

recoveries in typical lepromatous cases. The results obtained with the modern chaulmoogra oil parenterally in clearing up leprosy cases and bringing the disease under control in South Africa and in Nauru Island should also be referred to (*see* p. 335 and 337). *It is noteworthy that* in both Malaya and the Anglo-Egyptian Sudan, when the supplies of chaulmoogra derivatives were cut off during the second world war of 1939–45, the annual peace-time discharge rate fell to about nil. Nevertheless the chaulmoogra treatment of advanced infective lepromatous cases still leaves much to be desired.

Sulphones. The action of these drugs on the tubercle bacillus led to their trial in leprosy and remarkable results were observed in advanced lepromatous cases. **Promin** can only be given intravenously in daily doses, which limits its value, but Faget used it successfully in the U.S.A. **Diasone** is used orally in capsules or tablets beginning with a daily dose of 0·3 gm. increased to two or three such doses daily with two weeks rest after every two months. **Sulphetrone** is at least equally effective in oral doses of 1 gm. daily gradually increased to 3–5 gm. a day. With these preparations some improvement is usually seen in about one-fourth of the cases after six months, in 60 per cent. after one year and in nearly 100 per cent. after three years' treatment, so the improvement is slow and the preparations are costly.

D.D.S. or *Mother Sulphone.* *The above preparations* have complicated formulas, but the active principle of all is diaminodiphenylsulphone which costs about one-fifteenth as much. It was early reported too toxic for general use, but a three years' trial by Floch and Destombes enabled them to report very favourable results from doses of 40–200 mg. given orally three times a day, with rest on one day a week and for one week after every two months. Benefit was observed in all types among 101 cases, but especially in lepromatous cases. Both clinical and bacteriological improvement may be seen within two months ; shorter experience by others has confirmed the above findings. The cost of one year's treatment with this drug is little more than that of the chaulmoogra preparations.

Effects of Sulphones. Early effects include clearing up of nasal and laryngeal lesions, with great decrease in the infectivity of the patients, and the removal of the necessity for tracheotomy. Eye lesions also benefit. Nodules gradually shrink, but bacteriological improvement lags behind that of the clinical symptoms, so that after several years very numerous lepra bacilli may remain in the tissues and relapses have been noted, as the effects appear to be less on bacilli at a little distance from a blood vessel. During the earlier treatment reactions may occur, but do not necessitate the withdrawal of the drug unless unusually severe. Before long reactions cease to occur and so also do new lesions, such as repeatedly appear during the steady downhill progress of *untreated lepromatous cases. Thus bacilli entering the* blood stream appear to be killed and the well-known tendency of the

affected tissue slowly to decrease in favourable cases is assisted by the sulphone treatment. In some 50 per cent. of lepromatous cases the bacilli disappear from the tissues after four years' sulphone treatment. Sulphones are still more effective in early lepromatous cases, but are generally considered to be less effective in neural and tuberculoid patients, although good results have been reported in the last mentioned type.

Combined Sulphone and Chaulmoogra Treatment. In 1948 the complementary action in leprosy of these two classes of preparation was stressed by Rogers ; this suggests that both should be used at the same time. Thus in his early work in Calcutta he demonstrated that injections of hydnocarpates, with local reactions in the form of softening nodules, resulted in the break-up of enormous numbers of lepra bacilli into small red staining dots with or without febrile reactions, but with at times the disadvantage of distributing some whole bacilli through the blood stream to cause the production of fresh cutaneous lesions. On the other hand, the effect of sulphones is before long to prevent reactions, presumably by destroying any lepra bacilli which gain access to the circulation. It is therefore suggested that sulphones should be given for a few days before chaulmoogra preparations to allow any lepra bacilli entering the blood stream during local softening of nodules to be destroyed. Thus the very slow action of sulphones on lepra bacilli in the tissues might be hastened with advantage and recovery accelerated. Schujman has already reported that he obtained the best results in lepromatous cases by the combined use of these two classes of active remedies and the plan is being tested by others.

Treatment of Reactions. Tartar emetic intravenously is the most generally used treatment of excessive reactions. Fouadin in 2 c.c. doses intramuscularly has also been recommended.

The Red Corpuscle Sedimentation Test as a Guide to Treatment. Muir in Calcutta and Isabel Kerr in the Deccan found the sedimentation rate of great value in regulating the treatment of leprosy. Muir draws up 1·2 c.c. of venous blood from a patient into a syringe containing 0·3 c.c. of 5 per cent. sodium citrate solution ; the defibrinated blood is then drawn up into a 1 c.c. pipette graduated in hundredths, and stood upright in a rubber disc. The mean of the readings of the degree to which the red corpuscles have sunk at the end of two and three hours respectively gives the sedimentation rate. The normal is 10–20 per cent., but in active nodular cases it will be from 40 to 60 per cent. ; a high rate indicates an active disease necessitating caution in pushing treatment, and *vice versâ*. Some workers dispute the value of this test.

The Treatment of Complicating Diseases. Any co-existing disease of a curable kind, especially syphilis, hookworm infection or malaria, should be removed first, if good effects are to be obtained from treatment. The Wassermann test is unreliable in leprosy for the diagnosis of syphilis, but the Kahn test may be used, and if it is positive

penicillin treatment should be instituted. Carefully regulated exercise during the treatment is of great value, as in the closely allied tuberculosis. A generous diet, rich in all the vitamins, general hygiene, fresh air and cheerful surroundings and even encouraging suggestion, are of great value.

Excision of first cutaneous lesion has been followed by apparent cure for years in twelve out of fourteen tuberculoid cases in the Philippines and so is worth consideration in such early cases.

Perforating ulcers of the sole of the feet often show necrosed bone, which should be removed with good prospects of healing taking place.

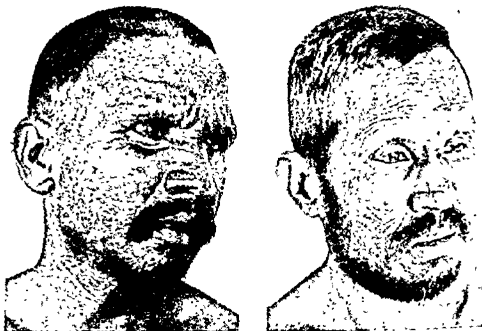


Fig. 53. Case of advanced lepromatous before and after treatment by injections of chaulmoogra oil derivatives by E. Muir.

Sympathectomy by division of the peri-arterial nerve fibres in Hunter's canal has been advocated, but is of doubtful value.

Decapsulisation of thickened ulnar nerves for severe pain only affords temporary relief, but slitting of the nerve sheath for cold abscess within it is of value.

Local applications to such ulcers include hydnocarpus oil or esters, sulphonamides, cod- or shark-liver oil, with a high vitamin A content, and painting with 1 per cent. solution of gentian violet in alcohol, followed by 10 per cent. silver nitrate in watery solution and then a 15 per cent. watery solution of tannic acid are advised by Muir.

Relapses are liable to occur if treatment is stopped too soon after apparent recovery, so it should be continued until negative examinations for lepra bacilli have accrued over a period of twelve months in lepromatous cases before discharge from a leprosarium. Re-examina-

tions for symptoms should be made every six months for five years for signs of relapse before the patient is released from observation. Relapses taken early usually respond to further treatment.

PROPHYLAXIS

Historical. Compulsory Segregation of all Types of Leprosy. From very early days the dread induced by the disfigurement of advanced leprosy and the fear of infection led to the adoption of life-long ostracism and rigid compulsory segregation of all types of the disease to a degree unknown in the case of any other chronic infection, although these drastic measures led to no effective reduction in the incidence of leprosy. A more humane and largely voluntary system of isolating the more infective types of the disease in Norway under exceptionally favourable circumstances enabled the disease to be reduced in the course of seventy years to only 5 per cent. of the incidence recorded in 1856 when this measure was begun. In the more backward stage of civilisation in tropical countries rigid compulsory segregation has failed in its purpose of materially reducing or stamping out leprosy in such countries as South Africa, the West Indies, Malaya, the Sandwich Islands and the Philippines. In the last-named country in 1906 the American sanitary authorities began a thorough trial of compulsory segregation at the Culion island settlement of all the discovered cases of leprosy with the immediate result of reducing greatly the cases seen at large in the towns. Yet three decades later the number of new cases discovered each year showed no appreciable reduction, and the main object of this heroic and costly measure was no nearer accomplishment.

Nor were the reasons for the failure of the measure far to seek, for as long as we had nothing better to offer the unfortunate victims of leprosy than permanent separation from their relatives and the world at large, with little or no hope of recovery and release, the patients naturally hid their affliction as long as possible, with the result that the average duration of their disease at the time of its discovery averaged five to eight years in both South Africa and in the Philippines. During this time they had infected some of the members of their households or their neighbours, thus maintaining the disease indefinitely.

The Scientific Basis of Improved Methods of Prophylaxis. A new era was opened up by work in Calcutta in 1915–17, confirmed and extended in 1919 by American workers in Hawaii, and elsewhere, which established the greater efficiency of the treatment of leprosy by injections of suitable preparations of chaulmoogra and hydnocarpus oils in place of the former oral administration of these nauseating drugs. It is, however, only in comparatively early stages of the disease that the improved treatment was effective in clearing up the symptoms in a considerable proportion of the cases, as was pointed out as early as 1917, so it became evident that the former rigid compulsory segregation,

with the resulting hiding of all the early cases, might do more harm than good, and epidemiological studies and surveys became necessary to ascertain how best to make full use of the improved treatment. Such inquiries brought about a clearer recognition of the facts that (*a*) most of the neural cases, including the recently differentiated tuberculoid form, are little if at all infective and seldom require isolation; and (*b*) that a large proportion of new infections occur among highly susceptible children residing in the same house as an infective lepromatous person; hence the necessity for the earliest possible detection of the disease by regular and frequent examinations of all contacts of known infective cases. The lepromatous cases should then be isolated in agricultural colonies and should receive skilled treatment. The writer therefore advocated the relaxation of rigid isolation of all types of leprosy and the adoption of measures modified to suit the local conditions in different countries.

The Principles of Modern Prophylaxis. (1) Isolation, of Infective ***Cases only, in Agricultural Colonies with a Minimum of Compulsion.*** (*a*) Where general compulsory isolation is already in operation the law should be modified, but not at first necessarily altogether repealed, to allow early cases of little or no infectivity to be treated as out-patients at already established hospitals and dispensaries, or, where cases are numerous, preferably at special dispensaries (which, in the Philippines, are called skin clinics) under a medical staff especially trained in the modern methods of treatment. British Guiana was the first of our colonies successfully to adopt this measure under F. G. Rose as the result of the acceptance of an offer by the British Empire Leprosy Relief Association (BELRA for short) to finance the construction of two leprosy dispensaries in the most affected areas, on condition that the compulsory law was relaxed as recommended. A number of hidden early cases soon came forward for out-patient treatment and infective ones were induced to enter the long-established leprosy settlement to obtain the best treatment. Within a few years the people had become so convinced of the value of the improved treatment that before long over half the admissions to the settlement were voluntary ones, with the result that in 128 out of 491 admissions the disease was arrested and its infectivity removed. A careful follow-up of the discharged patients showed that only 4·7 per cent. of the released patients suffered from relapses not readily yielding to further treatment. Fifteen years after the commencement of the new prophylactic measures E. Muir, as the result of a personal visit to British Guiana, was convinced that an actual decrease of leprosy in the colony had resulted, for the yearly number of new cases had fallen. Very similar results have been obtained in Ceylon.

In **South Africa** favourable financial conditions enabled the health authorities successfully to modify their century-old rigid system of compulsory segregation in a manner that is not feasible in poorer

countries. In 1923 their 2,501 segregated patients were examined bacteriologically and the one-third of them who were found to be negative were released as not requiring isolation. This allowed many known infected cases to be accommodated in the previously full institutions. The release of so many segregated cases for the first time; the gradual spread of the knowledge that an effective treatment of early cases had become available, and the provision of agricultural leprosy settlements in place of the long-condemned prison-like Roben Island Asylum at Cape Town, all combined to raise new hopes in the minds of the lepers. Soon an increasing number of early cases amenable to treatment voluntarily sought admission to the leprosy settlements for the sake of the improved treatment, which under the compulsory notification and isolation laws they could not obtain from private practitioners. With further releases of recovered cases this movement steadily increased with the result that fifteen years later, in 1938, the total number of patients who had passed through the settlements and been released with their disease arrested amounted to 4,502, or 66 per cent. of the total known cases in the Dominion of South Africa. Moreover, 2,738 of them had also been released from surveillance after having been re-examined at intervals for several years without having shown any sign of recurrence of their infections. In 1950 Winter recorded that the European patients in the leprosy institutions had fallen since 1913 from 190 to 56, a 30 per cent. decrease, and "coloured" from 345 to 75, or one-fifth of the former number. Further, the peak of 2,200 cases in 1944 had declined to 1,930 in 1949. Significant too is the decline in the duration of the disease on admission from 6·5 years, and probably higher, in 1926, to an average of only 2·4 years during the last 5 years; with greatly enhanced probability of successful treatment and of a steady further decline in the incidence of leprosy in South Africa.

(*b*) **In Countries with very limited Compulsory Powers.** In India only indigent lepers can be compulsorily segregated and the law is nearly a dead letter. About 10,000 patients are cared for in leper asylums, mostly under missionary societies with Government capitation grants, but a large proportion of these are advanced uninfective neural cases whose isolation is a charitable rather than a preventive measure. In 1920 the writer advocated the establishment in each province of one or more agricultural leprosy settlements to which only highly infective cases should be admitted under leprosy experts, together with the organisation of out-patient clinics for early cases at existing hospitals and dispensaries and at special leprosy clinics. Unfortunately, owing to lack of funds, little provision has yet been made to establish settlements during the last two decades, and the hundreds of leprosy clinics that have been provided have been of limited value, except those in charge of medical officers who have been trained in leprosy work. Where special dispensaries under trained staffs have been provided,

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incubation period is under five years, it is clear that the power to clear up a large majority of early cases gives us the means of reducing leprosy rapidly wherever the social conditions are sufficiently advanced to allow of the application of the following simple method. As soon as any case of leprosy is met with, all the members of the household and other close contacts should be examined from head to foot for the early signs of the disease. If this examination is repeated at least every six months for five years, 80 per cent. of infections from each patient should be detected, and 80 per cent. of these should be cleared up in the early curable stages. Theoretically this should allow the remaining foci of infection to be reduced in five years to 36 per cent., and in another five years to 12 per cent. of the numbers which existed in the previous decade ; much may therefore be done even if complete success is not obtained. As the average duration of life in the infective nodular cases is only about ten years, and most of the nerve and mixed cases will have passed the infective stage within that time, such a plan should rapidly eliminate the sources of infection, and new ones would in time become too few to be able to maintain the infection.

In the small Oceanic island of Nauru, Bray and Grant have reported the success of this measure in a very serious outbreak following the depressing influence of epidemic influenza combined with a deficient diet. An examination of the native population of the island in 1925 revealed leprosy infection of 30 per cent. of the 2,000 people ; within three years the number had been reduced by 40 per cent., and in nine years to under 17 per cent. by these measures. During this time scarcely any of the numerous early cases detected by the systematic examinations had gone on to the infective stage while under treatment.

Other Prophylactic Measures. Where leprosy is common the regular examination of all school children to detect and treat all cases at an early stage and to remove infective ones is an essential measure. In Uganda, infective children have been both treated and educated in a special institution with very beneficial results.

Separation of the sexes should be enforced wherever compulsory isolation is in force, but among primitive people induced to live voluntarily in agricultural colonies that measure is often impracticable. In Korea, Wilson permitted leper patients to marry and reside in special quarters after the males had submitted to be sterilised to prevent their wives bearing children ; each couple was allowed to adopt one leper child from the colony. Owing to the large proportion of leprosy patients who are first infected during childhood the protection of children of a community from infection is the most important single prophylactic measure.

Those affected with leprosy should be prohibited from following such dangerous occupations as the preparation and sale of food and clothing, domestic work, the care of children, nursing, including wet nursing, hair dressing and prostitution.

good results have been obtained as illustrated, for example, by the report for 1939 on the work in the Orissa Province. This records the treatment of 9,625 cases, mostly early, as out-patients with definite improvement at the end of a year in 90 per cent. of the patients at a very small fraction of the cost of institutional treatment.

(c) **In Countries in which Compulsory Segregation is Impracticable.** In the very extensive and highly infected leprosy areas of tropical Africa any attempt to enforce compulsory segregation of the cases nearly always defeats its own purpose by causing all types of cases to be hidden, but propaganda and surveys may pave the way to acceptance of effective measures by the people. The following are examples of the success of this policy. In the humid southern provinces of the Anglo-Egyptian Sudan, Atkey found on examining all the people 6,500 cases of leprosy, or 5 per cent., mostly early ones. Agricultural colonies thirty square miles in extent were supplied for 4,800 cases, including all the infective ones. They built their own houses and grew their food, so were self-supporting, and they received regular treatment. By 1934 the admissions numbered 7,075 ; and 3,679, a little over half, had been cleared of symptoms and infectivity. Still more important, yearly surveys showed very few new cases arising in the extensive area from which they had been removed. Very similar results were reported in 1946 with 54·4 per cent. of 2,689 cases recovered or quiescent, a steady decline in the yearly new cases found and a reduction in those under the age of twenty years from 24 to 12 per cent. ; all these figures indicate that the disease was under control and tending to decrease.

In Nigeria several large agricultural leprosy colonies have been established with a number of out-patient dispensaries grouped around them. With the cordial co-operation of the local chiefs, the people have constructed model leprosy villages in which all the advanced infective patients reside and receive treatment, while the earlier uninfective cases are treated in the dispensaries and further surveys are made from time to time to detect and treat new cases as they arise. For example, at the Uzuakoli settlement in the Owerri Province under T. F. Davey, within three years the dispensaries were increased from three to forty-four, the leper villages either opened or under construction numbered twenty-four, and 11,548 leprosy cases were being cared for by two medical men with BELRA and Toc H assistants, and a number of leprosy inspectors and male nurses were trained in the settlement. In one area the third survey revealed only forty cases, all early ones, among 7,000 people, the disease was under control and the plan was so popular that only additional staff is required to extend the work indefinitely. The practicability of these measures has thus been demonstrated.

(2) **Repeated Examination of Contacts to Detect and Treat New Cases in the Early Amenable Stages** (Rogers). When we consider that 80 per cent. of infections are house ones, and that in some 80 per cent. the

CHAPTER XVII

YAWS AND PINTA

YAWS

Definition. Yaws is a chronic disease of warm climates, caused by the *Treponema pertenue*. It is highly contagious by direct inoculation in any part of the body. Its causal organism closely resembles the *Treponema pallidum* of syphilis. It is non-venereal and occurs chiefly in children, but it runs the same general course as syphilis, and the same types of infective granulomata are formed in both diseases.

Distribution. Yaws is essentially a disease of warm climates. In early days yaws was very common in Negro slaves sent to the West Indies. It occurs in very large numbers of people throughout most of tropical Africa, and in limited areas of North and South Africa, including Algiers, Tripoli and the Sudan, in Ceylon, Burma, Southern Assam and in parts of Central and Southern India, but only in isolated foci in India as a whole. It is also found in the Malay States, East Indies, Thailand, Indo-China, the Pacific, Southern China proper, the Philippines and the northern coast of Australia and Oceana, in the West Indies and all northern South America, including most of Brazil. In some areas, such as Fiji, the Dutch East Indies, some Pacific islands and parts of British East Africa, nearly all the population suffer from the disease at some time in their lives, mostly during childhood, and they acquire considerable immunity after an attack. It is uncertain whether the disease originated in the Western Hemisphere or in tropical Africa (*see* Fig. 54 for the distribution in India and Burma). Yaws is more prevalent in rural than in urban areas.

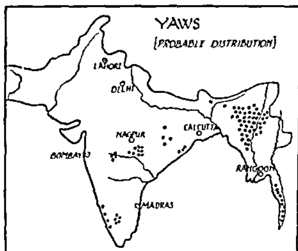


Fig. 54. Map of the probable distribution of yaws in India and Burma.

Ætiology. In 1905, A. Castellani discovered in unbroken lesions of yaws a delicate spirochæte indistinguishable in appearance from the parasite which Schaudinn had recently found in the closely allied disease, syphilis. Castellani subsequently demonstrated the organism

The above measures are being adopted increasingly in leprous countries. They constitute a great advance on general compulsory segregation of all types of leprosy, and have opened up the prospect of leprosy being materially reduced within two or three decades wherever it proves feasible to carry them out. Just as is the case in tuberculosis, so also in leprosy, improvement in the economic conditions of the community ought to form part of an organised campaign for the control of the disease.

LEONARD ROGERS

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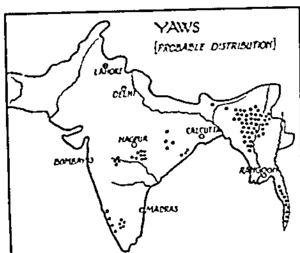


FIG. 54. Map of the probable distribution of yaws in India and Burma.

Ætiology. In 1905, A. Castellani discovered in unbroken lesions of yaws a delicate spirochæte indistinguishable in appearance from the parasite which Schaudinn had recently found in the closely allied disease, syphilis. Castellani subsequently demonstrated the organism

in the lymphatic glands and the spleen and also reproduced the disease in monkeys by inoculating them with material containing the organisms. On examination of fresh exudate from the lesions, using the dark-ground illumination method, a very thin motile organism, averaging 18–20μ in length and with six to twenty small uniform undulations, can be seen. It stains well with Leishman stain or by Fontana's silver method; the latter shows it up particularly well in the tissues. H. Noguchi succeeded in cultivating the parasite in ascitic fluid to which a piece of fresh kidney has been added, as in the case of the organism of syphilis. The spirochæte also grows in the deeper anaerobic layers of horse serum.

In monkeys inoculated with yaws the primary lesion appears after an incubation period of two to four weeks, but the lesion remains localised except in the Orang-Outang, in which a generalised eruption has been produced. No animals are known to be naturally infected with yaws. The disease can also be readily inoculated into man, the incubation period being twelve to twenty days.

Relationship of Yaws to Syphilis. This much discussed subject has been closely investigated by O. Schobl and by Hasselmann, who came to the following conclusions which appear to represent the more commonly held view on the subject. The spirochætes of the two diseases are morphologically, culturally and serologically indistinguishable, but they may be separated by their different biological behaviour in the body tissues. The parasite of yaws finds its home in the outer layers of the skin, but that of syphilis also attacks all the organs of the body; this difference explains the different pathology, immunity reactions, epidemiology, and clinical signs. In monkeys Schobl showed that yaws of some duration produces a cross immunity to syphilis, and this is in accordance with the experience of Lambert and others in the South Pacific that the widespread incidence of yaws protects to a large extent against syphilitic infection, although Schobl states that the two diseases may be present together in the same patient. Cases have been reported in which long-standing yaws has failed to confer immunity to subsequent infection with syphilis, and *vice versâ*. The Rockefeller Foundation workers of the Jamaica Yaws Commission, T. B. Turner and A. M. Chesney, after five years' investigations, found that the two diseases can be distinguished in their natural environment by their epidemiological and clinical features, and by the biological properties of their respective spirochætes. In inoculated rabbits and marmosets the lesions of yaws show striking and, for the most part, constant differences from those caused in these animals by inoculation with syphilis. Turner found a considerable degree of cross immunity in rabbits inoculated with *T. cuniculi* of rabbits, which is believed to be non-pathogenic to man. This raises the question whether the venereal spirochæte of rabbits might produce some immunity in man to other spirochætes. Yaws is rarely congenital and produces far less tendency

to abortion than syphilis, as shown by the studies of G. C. Butler in the Accra maternity hospital in West Africa. Tabes dorsalis and general paralysis of the insane are very rare late complications of yaws. On the other hand, D. B. Blacklock is of the opinion that the differences in the clinical and pathological manifestations of yaws and syphilis do not suffice to distinguish between them, but van Notsen disputes all the statements on which Blacklock based his arguments. As the treatment is much the same the controversy is of more academic than practical interest.

Under the term **Bejel**, E. H. Hudson has described a non-venereal form of syphilis among the Arabs of the middle Euphrates, which he thinks is intermediate between syphilis and yaws.

Pathology. The primary lesions are congestion of the epidermis, œdema and infiltration with polymorphonuclears, lymphocytes and histiocytes. Similar changes are seen in the secondary lesions; but there is also enlargement of the epidermal ridges due to inflammatory infiltration which barely extends beyond the limits of the dermal papillæ. The changes are held by some workers to differ from those of syphilis in being less extensive and in not affecting the blood vessels, but members of the Jamaica Commission found histological criteria unreliable for the differentiation of the two diseases.

Transmission. The primary lesion in yaws is extragenital in 99 per cent. of cases. The disease is very contagious, and under conditions of overcrowding and insanitation the infective discharges from a case are readily inoculated into any abrasion or wound in a susceptible person. Personal contagion is therefore the usual condition which is necessary to the conveyance of infection. Flies and other insects may also carry the organisms from the sick to the healthy, but the spirochætes cannot pass through the intact skin. In Nyasaland W. A. Lamborn infected a native volunteer with spirochætes in a regurgitated drop of fluid of the fly, *Musca sorbens*, which had been fed on a yaws sore. The Jamaica-Commission worker, H. W. Kumm, found that the minute fly, *Hippelates pallipes*, which swarm in thousands on yaws ulcers, may transmit the spirochæte through the regurgitation of fluid from the anterior part of the gut, in which the organism can live for seven hours; he and T. W. Turner successfully infected rabbits in this way.

Age. Children and young people are most often infected, 91 per cent. of cases in Jamaica being under fifteen with the largest number at the age of seven years, but no age is exempt and sex makes no difference. Native races are said to be more susceptible than whites. Children with yaws may readily infect their mothers; in these respects, again, the disease differs from syphilis. The disease does not spread in cold climates or at high elevations in the tropics where the air temperature is low. Thus H. D. Chambers found a very close relationship in Jamaica between high humidity and rainfall and high incidence of yaws; this was not the case with syphilis. Probably the skin must

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be damp with perspiration if infection is to be conveyed under natural conditions. The more civilised people of the tropics are practically exempt, probably because of the greater cleanliness of their personal habits.

Clinical Description

The incubation period is said to vary between two and four weeks, during which there may be slight fever and a feeling of illness, together with headache and pains of a rheumatic type.

The primary lesion appears at the end of the incubation period at the site of inoculation of the spirochæte, which may be situated on any



Fig. 55. West Indian yaws (Sambon). (Wellcome Museum of Medical Science.)

part of the body, but is most frequently met with at the site of an abrasion, including skin areas liable to be scratched, an ulcer, an insect bite or even a vaccinia pustule. In women infection often occurs from contact with the infected child, and the sites of election of the primary sore are the breast, the bend of the elbow, or just above the hip ; these being the places with which the closest contact is made when the child sucks or is carried about by the mother. The primary lesion is usually single, but may be multiple ; it closely resembles the lesions of the second stage ; it is sometimes known as the mother-yaw. It begins as a papule or as a vesicle, and soon enlarges to the size of a pea through cracking of the skin and exudation of a serous discharge, which dries to form a raspberry-like scab about the size of a pea ; on

the removal of the scab a small granulating ulcer is seen, which eventually heals and leaves a white or pigmented scar. Some degree of fever and general pains occur with the appearance of the lesion, and indicate the existence of constitutional disturbance; diarrhœa and gastric disturbance may occur, especially in children. The duration of the primary lesion is very variable; it may disappear before the generalised secondary eruption appears, or it may persist, together with the secondary lesions, for several months. The nearest lymphatic glands may become hard and tender, but suppuration does not occur.

The secondary stage commences in six to twelve weeks after the appearance of the primary lesion, and is accompanied once more by irregular intermittent fever, headache and pains in the joints, bones, and muscles. The eruptions are now multiple and their appearance may be preceded by patches of fine furfuraceous desquamation, on



FIG. 56. Case of yaws showing generalised distribution of granulomata. (After Lopez-Rizal and Sellards.)

which, after a few days, small papules appear and develop into lesions similar to those of the primary lesion. The sores cause a good deal of itching, but are not painful, and smaller lesions often appear around the larger ones. The eruptions vary in size from that of a small pea up to that of a walnut, and stand out prominently as numerous light-yellow raspberry-like crusts resulting from the drying up of serous discharge. The appearance of the lesions is very characteristic (*see* Fig. 55).

The distribution of the eruption is very variable, but it tends to occur particularly on the face, neck, extremities, buttocks, perineum, and in the axillæ. On moist warm parts it may resemble the condylomata of syphilis (*see* Fig. 56). The lesions are less numerous on the trunk and quite uncommon on the scalp. Secondary lesions may persist for several months or up to two or three years. Each lesion tends to heal after a few weeks, and fresh papules appear in succession, but the constitutional symptoms and fever do not persist after the

appearance of the secondary rash. The eruptions heal by drying up and dropping off of the crusts, underneath each of which a white scar is left ; this may later become pigmented, just as is the case with the primary lesion. Painless enlargement of the lymphatic glands accompanies the secondary eruption. Fluid taken by puncture of the glands contains the spirochætes, and the Wassermann reaction becomes positive at this period of the disease. Papular, scaly and ulcerative varieties of the eruption may closely resemble syphilitic lesions. Castellani describes in this stage small granulomata of the tongue, nasal mucous membrane and vagina, as well as affections of the joints, bones and muscles, but other authorities state that the mucous membranes are not involved.

The tertiary stage shows a much greater variety of lesions, and there is still some difference of opinion as to whether certain clinical manifestations and complications should or should not be included under the term " tertiary lesions." Gummatous nodules may appear in the subcutaneous tissues, and break down to form indolent ulcers, or the granulomata may break down to produce irregular spreading chronic ulcers, which may be followed by contractures and deformities of the extremities or other parts of the body. A very painful and crippling condition, known as clavus, may result from the formation of nodules beneath the hard skin of the feet. These lesions may ulcerate and produce erosions or deep fissures.

The bones are also attacked by tender nodes of the periosteum, which resemble gummata ; these chiefly affect the long bones of the extremities. Diffuse painful osteitis sometimes occurs and X-rays may reveal oval rarefied areas in the long bones, which are liable to spontaneous fractures. In Australia C. J. Hackett observed rounding of the tibial crest called boomerang- or sabre-leg. Curvature of the little or ring finger may also be a late symptom.

Juxta-articular nodules are multiple fibrous painless swellings up to 2 or 3 inches in diameter in the neighbourhood of the joints, especially of the knees and elbows. Spittel, of Colombo, pointed out that these nodules are tertiary lesions of yaws, and not a distinct disease. Chronic synovitis has been recorded in some cases.

Gangosa is another condition which is now believed to be a tertiary manifestation of yaws. It is characterised by chronic ulceration of the mucous membranes of the nose and pharynx, with extensive destruction of the hard palate and of the cartilages and bones of the nose. Eventually there is great loss of tissue, and the nose is replaced by a pit-like cavity whose bottom opens into the mouth. This condition may occur at any age ; it is most common in Oceania and in the East and West Indies, including British Guiana. It may simulate the extensive syphilitic ulceration which sometimes occurs in the same region of the body.

Prognosis. Under modern treatment this is very good ; in the

primary and secondary stages, but in the tertiary stage progress is much slower and more prolonged treatment is required. Much deformity may result in cases which come under treatment after tissue destruction has taken place. The direct mortality of the disease appears to be very small.

Diagnosis. In the endemic areas large numbers of cases are seen, and there is no difficulty in recognising the presence of yaws. In some of the Dutch East Indian and Oceanic Islands 70 per cent. or more of the inhabitants have suffered from the disease. The primary and secondary lesions are so characteristic that the diagnosis is easy, and, besides, the causative spirochæte can usually be found in the serum obtained by puncturing unbroken yaws lesions. In the tertiary stage, with ulceration and gumma formation, the diagnosis of the ulcerations and gummata from syphilis is far more difficult, especially as the Wassermann test is positive in both diseases, and the causative parasites, which are difficult to find, are similar to those of syphilis. Yaws differs from syphilis in not being congenital, in its failure to yield to mercury treatment, in the extra-genital situation of the primary lesion, in the early appearance of nodular secondary lesions, in the itchiness of the nodules, and the frequency of the disease in children below the age of puberty. These points assist in the differentiation, but there are cases in which great difficulties may arise, and it is quite certain that the two diseases are very closely related to each other. One writer has aptly described yaws as "stone-age syphilis." Yaws does, to some extent, appear to take the place of syphilis among many primitive peoples.

Treatment

The introduction of neoarsphenamine and allied preparations has revolutionised the treatment of yaws. It should be given in doses varying from 0·1 gm. in very young children to 0·6–0·9 gm. in adults. In the very young it may be injected intragluteally in a 0·4 gm. dose in oil. By either method three to six doses given weekly are necessary to lessen the danger of relapse. In tropical endemic areas it is more economical to give sulpharsenol in doses of 0·1–0·6 gm. intramuscularly or subcutaneously. Stovarsol or acetarsone orally in 0·25–1 gm. tablets before food in the morning on alternate days for about a fortnight is also a useful method.

The high cost of the salvarsan group of remedies is prohibitive when many thousand cases of yaws have to be treated, so that in British East Africa **bismuth salts** have been substituted ; the results have been excellent, and there has been a very great saving in expense to the administration. Bismuthotartrate of sodium and potassium in doses of 0·2 gm. in freshly-prepared and boiled solutions are given intramuscularly at the cost of one-tenth of a penny a dose. A careful watch must be kept for symptoms of stomatitis ; this should be treated by

the local application of 5 per cent. methyl violet and by 0·5 gm. ascorbic acid intravenously for ten days if severe.

Bismuth sodium tartrate of Howard under the name of **Sorbita** has also been found effective in 3-grain doses dissolved in 40 minims of sterile distilled water and injected into the gluteus muscle ; it costs less than one farthing a dose, and the results are nearly equal to those obtained with the expensive arsenical preparations, both for secondary and tertiary cases. Bismuth salicylate was recommended as an efficient and cheap form of treatment by the Jamaica Commission. It can be used in the form of the Injectio Bismuthi Salicyatis (B.P.), which contains 10 per cent. of that salt suspended in a sterile solution of camphor 1 per cent., and phenol 1 per cent. in olive oil. The dose is 10–20 minims intramuscularly.

A combination of bismuth and arsenic in the form of bismuth



FIG. 57. Yaws in a child before salvarsan treatment.



FIG. 58. Yaws in a child after salvarsan treatment.

arsanilate suspended in oil and injected intramuscularly has been recommended by R. N. Chopra and others in doses containing 1 grain in 15 minims. When practicable the treatment should be continued until the Wassermann reaction becomes negative in order to obtain permanent results. Mercury is useless in any stage of yaws.

Local treatment consists in cleanliness and the use of antiseptics to keep the sores from becoming septic and to allay irritation. Perchloride of mercury, 1 in 1,000, may be used or boracic acid.

Penicillin has proved to be even more effective than the foregoing drugs in the West Indies, Africa, etc. The causative *Treponema pertenue* disappears from the tissues within one or two days without any serious reaction and the lesions all heal in about one month. From 15,000 to 30,000 units should be injected every three to four hours up to a total of one to two million units in hospital patients. For out-patients 100,000 to 300,000 units of calcium penicillin, and relatively

smaller doses for children, in peanut-oil with 4·8 per cent. beeswax are injected at twelve-hour intervals on the same day or on two consecutive days, which allows of large numbers being dealt with. In Haiti *apparent cure was thus obtained in 90 per cent. of cases with only* 2 per cent. of re-infections. This treatment promises to allow of yaws being rapidly brought under control at a reasonable cost. Negative Wassermann reactions have not been obtained more rapidly than after the use of arsenical preparations, so it has been suggested that the latter should also be given to lessen the danger of relapses.

Control by Survey and Treatment. In the Belgian Congo large-scale treatment of yaws for several years has resulted in a rapid reduction in the incidence of the disease. The Jamaica Commission also found this to be a practical method of yaws control. The number of infectious cases diminished very rapidly up to six months, and more slowly afterwards, and at the end of one year the attack rate was diminished by 87 per cent. ; and 8 per cent. more with neoarsphenamine than with bismuth : and more after six than with four doses. A follow-up showed that one-third of the cases relapsed within two and a half years and required further treatment. A positive Wassermann reaction was reversed after six months in 22 and 47 per cent., and after three years in 60 and 72 per cent., with arsenic and bismuth respectively.

Prophylaxis. Isolation of yaws patients has been practised in the West Indies and elsewhere ; but with a large number of cases efficient treatment to reduce the foci of infection and the protection of wounds and abrasions from infection by contact or by flies are the most effective measures.

PINTA (*syn.* CARAATE)

Definition. Pinta is a spirochætal disease characterised by multicoloured skin lesions.

Prevalence and Distribution. Pinta is found in tropical America, notably in Cuba, Venezuela, Mexico, Colombia and Bolivia.

Ætiology. Until recently regarded as due to parasitic fungi, Pinta is now known to be caused by a spirochæte *Spirochæta herrejoni* (*carateum*) allied to the causative organisms of syphilis and yaws, and morphologically indistinguishable from them. It is readily demonstrable in the skin lesions. Previous infection with syphilis does not give complete immunity against Pinta.

The disease is contagious and may be spread by flies.

Pathology. No characteristic visceral lesions have been found. Spirochætes may be demonstrated in the corium of the skin and in the lymph glands draining the affected area. The Wassermann and Kahn reactions are positive.

Symptoms. In pinta produced experimentally by inoculation from a patient an initial papule appears after an incubation period of from one to three weeks. This papule gradually enlarges and is followed

after a variable interval by crops of pintids or secondary erythematous lesions. The pigmentary functions of the skin are grossly disturbed with the result that areas of hyperpigmentation, hypopigmentation and depigmentation run into one another, varying in colour as the disease progresses. Hyperkeratosis of the soles of the feet and of the palms of the hands is frequently found. The patient may suffer from a severe degree of pruritus and, as a result of constant scratching, may produce chronic running sores.

Diagnosis. Skin biopsy is necessary to confirm a clinical diagnosis.

Treatment. Penicillin has replaced organic arsenic and bismuth as in the case of syphilis.

LEONARD ROGERS

CHAPTER XVIII

TROPICAL ULCERS AND OTHER LOCAL CONDITIONS

DERMAL LEISHMANIASIS, OR ORIENTAL SORE

Definition. Granulomatous nodules of the skin and mucous membranes, which usually ulcerate, are caused by the protozoal parasite *Leishmania tropica*.

Historical. D. D. Cunningham in 1885 found darkly-staining "parasitic bodies" in the mononuclear cells in cases of "Delhi boil." The coloured illustration of these shows clearly that they were Leishmania bodies. As recently pointed out by C. A. Hoare, P. F. Borovsky in 1898 first recognised the parasite to be a protozoon, and in 1903 J. H. Wright, in America, described their characters and identified them as protozoa. Soon after the cultivation of the closely similar *Leishmania donovani* of kala-azar the parasite of oriental sore was also grown by Nicolle in the water of condensation of neutral blood-serum agar, and more recently the Sergents have shown that the infection can be conveyed by local inoculation with the crushed bodies of sandflies which contain the flagellate forms of the parasite, and Adler and Theodor have reported the development of an oriental sore at the site of the bite of an infected *P. papatasii*. In Italy *P. perfiliewi* (*P. macedonicus*) has been found to be the carrier.

Distribution and Epidemiology. The terms Delhi, Lahore, Bagdad, Aleppo and Biskra (Algeria) boil indicate some of the places where the disease is most common. It is prevalent in China and from the Punjab and North-west Frontier Provinces of India throughout South-west Asia, including Palestine and Arabia, in Egypt along the camel track to Palestine and South Russia, the northern countries of Africa down to the Sudan and West Africa, and occasionally north of the Mediterranean Sea, as in Crete and Italy. An American form, in which there is a great tendency to ulceration of the mouth and pharynx, is known as espundia. This is prevalent from Mexico and Costa Rica in the north to Argentina in the south. It is very remarkable that the great areas of kala-azar in the eastern provinces of India and north of the Mediterranean are nearly free from this form of dermal Leishmaniasis, but the distribution of the carrier sandflies, and the climatic conditions favouring the development of the parasites in them, are likely to afford the clue to this peculiarity (*see* Fig. 59). In Palestine, T. Canaan found that 78·5 per cent. of oriental sores appear in the summer and 21·5 per cent. in the autumn and early winter in accordance with the practical disappearance of sandflies from December to April.

Great local variations occur in the frequency of the disease. In

Bagdad nearly everyone is attacked, usually in childhood. One village may suffer greatly and a neighbouring one little or not at all. There may be great variations from year to year in the same locality, the disease being common in one year and rare in the next.

Ætiology and Pathology. The *Leishmania tropica* is indistinguishable microscopically from the *L. donovani* of kala-azar already described (*see* p. 63), and it also develops into the flagellate stage in the same culture media. Sandflies were first suggested to be the carriers of the infection by C. M. Wenyon, who in 1911 found 6 per cent. of these flies in Allepo infected with flagellates of the Leishmania type. In 1921 the Sergent brothers in Algeria infected persons in a non-endemic area by applying flagellates of *Phlebotomus papatasii* brought from an endemic area of the disease. In 1925 S. Adler and O. Theodor in *Palestine traced the flagellate stage of the parasite to the mouth parts* of sandflies, and in 1941 they obtained much more frequent infections of man through the bites of *P. papatasii* fed through a membrane on

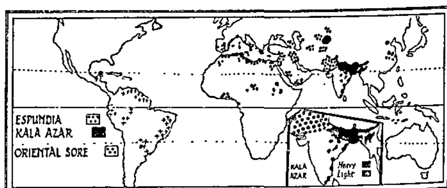


Fig. 59. Map of world distribution of Espundia, Kala-azar and Oriental Sore.

a suspension of flagellates in saline and blood with a high salt content and kept at 30° C. They also found oriental sores to be much more common in a Dead Sea area with soil of a high salinity.

Dogs, cats, bears, and, in Russian Turkestan, gerbils, *Rhombomys*, to the extent of 60 per cent. of the animals, as well as marmots have been found naturally infected with oriental sores ; monkeys, mice, etc., have been artificially infected. J. A. Sinton has infected a man after a long incubation period by the inoculation of nasal mucus containing the parasite in North India where *P. sergenti* is the vector. Sandflies are readily infected by feeding on oriental sores. Mechanical transmission by flies is also possible.

Clinical Description. In the early stage a papule or papules are produced after an incubation period which is said to vary from a few days to several months ; in experimental inoculation it is usually from three weeks to four months. The lesions may be single or multiple, and are met with chiefly on exposed parts of the body, such as the face, tongue and extremities. Before long superficial ulceration usually

occurs, but the margins of the ulcers are raised and hard; the parasites are situated in the margins and deep in the floor of the ulcer. The tissues round the sores show a small-round-celled infiltration. The sores vary widely from small non ulcerated papules to large ulcers or even warty growths, and the diagnosis can only be made with certainty by finding the parasites either in deep scrapings from the floor of an



FIG. 60. Multiple Oriental Sore in an Arab. (Wellcome Museum of Medical Science.)

ulcer, or, better, by puncturing the thickened margin through the skin with a hypodermic needle or a fine-pointed glass pipette whose tip has been broken off, and staining smears by the Leishman method, or the material may be used for making cultures in N.N.N. medium. The puncture is best made through non-ulcerated skin to avoid bacterial contamination.

After a duration of several months spontaneous healing usually takes place, and a considerable degree of immunity results, so that in

Bagdad the disease was frequently inoculated on the extremities of children to protect them from the disfigurement which would be likely to result from naturally-acquired sores on the face. In experimentally-inoculated cases in Palestine self-healing took place in three to seventeen months. The surface of an ulcer is often covered with a scab, and the discharge is small in amount unless there is a secondary bacterial infection ; *the margin is clear-cut, and there is not much pain.* The neighbouring glands are not enlarged unless suppuration occurs. Healing commonly takes place under a scab formed by the drying up of the discharge, and eventually a permanent white scar with some contraction remains. Apart from secondary infections, the disease is not dangerous, but it may cause considerable disfigurement of the face (*see* Fig. 60).

Prophylaxis. Protection from sandflies is important but difficult, as they pass through mosquito curtains. Sores should be covered to protect them from insect carriers.

The Prognosis is good as far as life is concerned, but the disease is long and troublesome.

Diagnosis. The causative parasite is most readily found in serum squeezed from a portion removed from the edge of the ulcer. Cultures may be obtained by the addition of penicillin to destroy bacteria as it has no action of the *L. tropica*. In cases in which the parasite is not readily found microscopically A. Donatien and F. Lestoquard advise the use of the formol-gel test. A. Distrowsky failed to find the parasite in 23 per cent. of Palestine cases, but obtained 97 per cent. of positive reactions to the intradermal injection of 100,000 cultivated *L. tropica* in 0·1 c.c. of 5 per cent. phenol ; in positive cases a papule not less than 0·5 cm. in diameter appeared within forty-eight hours. Recovered cases also react. A similar reaction has been obtained in the S. American form in 97·7 per cent. of cases by Montenegro and others.

Espundia is a tropical American form of the disease which differs in that the oro-nasal mucous membranes are involved in the ulcerative process in some 80 per cent. of the cases. The causative organism has been named *Leishmania brasiliensis*, although it is indistinguishable from *L. tropica* except possibly through serological tests. It is met with from Mexico in the north to Argentina in the south, and it affects as many as 20 per cent. of the people in some parts of Brazil. Dogs and the Texas ground squirrels, *Citellus tridecemlineatus*, can be infected with the disease and it is believed to be transmitted by sandflies. The duration of the disease varies between four months and four years, and one attack produces immunity. The Montenegro skin test is of value in diagnosis ; it consists in the development of a papule within forty-eight hours of the intradermal injection of an antigen prepared from cultures of *L. brasiliensis* ; the papule persists for four or five days. Vaccines prepared from cultures of the causative parasite have been reported by Brazilian workers to produce some degree of resistance

against infection. The treatment is the same as for oriental sore. Cases of ulceration of the oral mucous membrane have been reported in the Sudan and Kenya.

Treatment

It was in the American form of this disease that G. Vianna, in 1913, found intravenous injection of tartar emetic to be a specific against Leishmania infections. Potassium or sodium antimony tartrate is still regarded as the best treatment. These salts are given in the same way as in the treatment of kala-azar (*see* p. 76), but they fail in some cases. A total of 20–30 grains in ten to twenty injections is required to clear up the lesions ; less scarring results than after natural healing. In Palestine no case resisted tartar emetic treatment, and healing took place in an average of ninety days. Other antimony preparations that have been reported to be effective are **neostibosan** as used in kala-azar (*see* p. 77), and **fouadin** intramuscularly in doses of from 0·5 to 5 c.c. The local application of 1–4 per cent. tartar emetic in vaseline, with 3 per cent. cocaine to reduce irritation, is of value.

Emetine hydrochloride was found by Photinos to be effective if injected in doses of from 0·13 to 0·75 grain around the edge of the ulcer with healing in two to four weeks ; or up to 20 minims of a 5 per cent. solution may be injected into the edges and floor of the ulcer. **Berberine sulphate** has been found by several observers in India to be rapidly curative on injection close around the edges of the sores in doses of 2 c.c. of a 1 per cent. solution after one to three treatments. Das Gupta in Calcutta found that a 1 in 80,000 solution inhibited the growth of both *L. tropica* and *L. donovani*.

Local treatment may also be effective, the most successful in India being the application of carbon-dioxide snow for five to thirty seconds every ten days. F. Holmes, in Quetta, advocates mass treatment by scraping the ulcers and nodules under gas anæsthesia followed by the application of pure carbolic acid and covering with elastoplast for two weeks. X-rays, infra-roentgen rays, zinc ionisation and diathermy all have their advocates. An ointment consisting of equal parts of camphor, olive oil and beeswax is reported by Laguer to produce healing in one to four weeks, but it is contraindicated in sores affecting the nose or eyelid. In Bagdad H. Akrawi reported on seventy-two ulcerating oriental sores treated by local applications of sulphonamides ; there was cure without scarring in 63 per cent. of the cases within a month.

Vaccines of *L. Tropica*. In the Punjab J. D. Varma reports cures in twenty-five of thirty-five cases treated by injections of 0·5–1 c.c. doses of a vaccine made from cultures of *L. tropica* prepared by J. C. Ray. Prophylactic subcutaneous injections of living cultures on an arm or leg, to produce an immunizing oriental sore where it will not cause disfiguration, have been used successfully in about 500 persons in South-east Russia and in Palestine.

INGUINAL ULCERATIVE GRANULOMA

This is a somewhat rare form of chronic ulceration which occurs in various tropical countries. It appears to result from sexual intercourse. The ulceration involves the inguinal region and neighbouring parts. In India it is most frequently seen in Madras, and it has been met with in Oceania, Tropical America, including the Southern United States, *Africa, China and North Australia.* The Negro and other indigenous races are more often attacked than Europeans, and males more frequently than females.

Ætiology. This is still unsettled ; the most probable cause is the body, *first described by C. Donovan, in Madras, in 1905, as occurring* in the large mononuclear cells of the lesions, but the nature of this has given rise to much speculation. J. A. McIntosh and others consider



Fig. 61. Typical case of granuloma inguinale showing multiple lesions on penis, groin and scrotum.

the body to be a short capsulated bacillus of the Friedländer group, but M. F. Campbell and others have failed to reproduce the disease by inoculation of this organism, so proof is wanting of its ætiological relationship in spite of its frequent presence in the lesions. De Monbreun and Goodpasture have cultivated a bacillus of the aerogenes group from two cases with organisms which showed all the morphological appearances of the Donovan bodies, including the *development* of a resistant capsule, so they consider it requires further investigation. Infection most likely takes place through sexual intercourse, but probably an abrasion of the skin is necessary to allow the entrance of *infection ; the ulceration appears to spread* to neighbouring parts by auto-inoculation (*see* Fig. 61).

Clinical Symptoms. The first lesion is usually a papule on the penis or the labium minor, it appears from two to eight days after sexual intercourse, and soon grows into a superficial ulcer. The most

characteristic feature is the great tendency for the lesions to extend slowly, and to involve extensive areas of the moist parts of the groin and perineum in a butterfly-shaped superficial ulceration; in the female the ulcer may spread into the vagina and sometimes produces a rectovaginal fistula. The surface is red, the discharge thin, and the lymphatic glands are not enlarged except as the result of secondary infections. Healing may take place in one part, while the ulceration is spreading in another; the course of the disease is very prolonged and may extend over several years, pain is slight, but stricture of the urethra or pseudo-elephantiasis of the genitals may result although the general health is little affected.

Diagnosis. Microscopical examinations of excised portions may be necessary to allow the condition to be differentiated from epithelioma or lupus, but the latter is very rare in the inguinal region, and the absence of response to salvarsan and negative Wassermann reaction will help to distinguish the disease from syphilitic ulcers. The diagnosis may be of great importance to the patient, as cases have occurred in which amputation of the penis has been done on the assumption that the disease was an epithelioma.

Treatment. Formerly this was very unsatisfactory, as local applications and scraping the ulcer were followed by recrudescence of the disease. Antimony treatment as for leishmaniasis is effective in most cases of this disease, although occasional failures are met with. In some of these X-ray therapy has proved effective, but sometimes this treatment also fails. Cleansing with eusol solutions and touching with silver nitrate are of value. Favourable results have been reported following fouadin intramuscularly, combined with penicillin or streptomycin. Injections of streptomycin, 4 gm. daily in divided doses four hourly for five days, have been found very effective. If the case is recognised early complete excision of the primary nodule before extension of the infection has occurred will usually be effective.

TROPICAL ULCER

Tropical ulcer, or tropical phagedena, is common in a number of very humid tropical countries, such as Assam, where it occasionally assumes epidemic proportions, and causes great economic loss on tea estates by incapacitating numbers of the labour forces for long periods. It is prevalent in South-East Asia from India to China, in the South Pacific, tropical Africa and in the West Indies and much of South America.

Its ætiology is still unsettled, but the ulcerated patches contain innumerable darkly-staining large fusiform bacilli of the Vincent type, together with fine lightly-staining spirochætes. Anaerobic cultures on ascitic fluid agar at 37° C. show large bacilli of the Vincent type during the first few days, after which fine spirochætes predominate. The

organisms may be stained by the Giemsa method, or in the tissues by Fontana's silver nitrate technique.

Human volunteers and monkeys have been inoculated with the disease at sites of local injury. Flies may carry the infection.

Predisposing Causes. *Debilitating conditions and lack of cleanliness* may favour infection. Diet is important for the disease is comparatively rare among those on a good protein diet such as meat, milk and fresh vegetables, but common where vitamin A is deficient. The addition of foods containing carotene and ascorbic acid favours healing of the ulcers.

Symptoms. The ulcers are usually situated on the lower part of the legs and on the feet, but the upper extremities and other exposed parts of the body may be attacked. Ulcers develop at the sites of abrasions and insect bites. A painful pustule first forms ; this rapidly develops into a round or oval, spreading, sloughing ulcer from the floor of which pus is discharged. The ulcer may become widespread and serpiginous ; sometimes it becomes so deep that it involves the muscles, tendons and periosteum. The disease runs a chronic course of some months' duration with ultimate extensive scarring and even contractions ; the ulcer may extend right round the leg and be very difficult to deal with ; sometimes amputation is necessary.

The **diagnosis** is usually made on clinical grounds confirmed by the presence of the causative bacilli.

Treatment. Antiseptics of various kinds are recommended for this troublesome condition. The first step usually is to scrap the ulcer under an anæsthetic, and then to swab with pure carbolic acid. Other applications are : frequently renewed dressings with 1 in 1,000 perchloride of mercury, strong formalin. acriflavin, 1 in 500 solution of copper sulphate, or 1 in 500 permanganate of potash, or baths of 1 in 5,000 strength. As any of these applications are liable to be painful injections of morphia may be required for a time. *Peroxide of hydrogen* acts in a similar manner by destroying the toxins, and Carrel-Dakin solution has also been advised. E. J. Blackaway reports from Nyasaland rapid cure of old-standing cases by the use of Sayers' method of applying strapping, such as elastoplast, over zinc oxide directly over the ulcers for fourteen days. The healing of extensive ulcers, once they show healthy granulations, may be hastened by the use of Thiersch skin grafts.

The **sulphonamide** group of drugs dusted over the ulcers have been recommended, especially in the early stages. Cod-liver oil or whale-oil, 30–40 per cent. in vaseline, locally, has also been advised.

Diet. In Uganda L. J. A. Loewenthal found that tropical ulcer is not seen in the well-to-do who take milk and meat in their diet, but only in the poor living on a deficient diet containing little calcium. On treating cases in adults with intravenous injections of 15-grain doses of calcium chloride in 10 c.c. distilled water the offensive odour was soon

lost and the sloughs cleaned up in ten days followed by rapid healing provided rest in bed was maintained.

Penicillin is reported to be effective in this troublesome condition. Local application on gauze should be reinforced by intramuscular injections. Fever and inflammation is reported to subside within three days, accompanied by cleaning up of the ulcers to present a granulating surface, to which strapping can be applied. Aureomycin may be even more effective.

Prevention. Protection of the feet and legs by boots and putties is believed to be useful, as the infection enters through a local injury by stubble, the sharp points of pruned branches, etc. Frequent washing of the feet and legs with permanganate lotion or other antiseptic may be effective.

VELD OR DESERT SORE

This term has been applied to a form of ulcer that occurs mainly in dry or desert areas, as opposed to the humid climates in which tropical ulcer develops, and it has been met with chiefly in North Australia, North and South Africa, the Sudan, and in South-west Asia.

The ætiology is uncertain and numerous organisms have been described. Some of the ulcers are caused by the diphtheria bacillus, when anti-diphtheritic serum is an effective form of treatment. Diphtheritic neuritis and paralysis may occur and the bacilli may sometimes be found in the throat ; later staphylococci and streptococci predominate. There is generally a history of preceding scratch, abrasion or insect bite. Work attended with much perspiration is a predisposing cause.

Symptoms. The disease commences with the formation of a very painful blister on an exposed part of the body, usually the extremities or face. The blister bursts and lays bare a superficial rounded ulcer with thin serous discharge and a grey or red base, and this may extend with an irregular thickened and undermined margin. The course is often very prolonged, from one to twelve or more months. The ulcers are frequently multiple and leave thin white scars.

Treatment. Antidiphtheric serum in doses of not less than 20,000 units should be injected around the sores, and may prove rapidly effective even in long-standing cases. In the early stages simple dressings, such as eusol, suffice. Applications of cod-liver oil have been advised. In North African campaigns 3 per cent. sulphanilamide or sulphpyridine in soft paraffin proved of value in clearing up secondary coccal infections. The isolation of cases showing diphtheria bacilli lessens the spread of the disease. Penicillin as a local application is effective in cleaning the ulcers. Dressings of antiseptic lotions, such as permanganates, should be applied to the sores. In areas where these sores are prevalent all abrasions should be treated with antiseptics as a prophylactic measure.

MYCETOMA, OR MADURA FOOT

This is a chronic inflammatory disease of the foot, but sometimes of the hand, knee or other part of the body. It is caused by the invasion of the tissues by certain kinds of fungi. There is swelling and deformity of the affected part with a gradual progressive degeneration of the deep structures. On the surface of the limb there are granulomatous nodules ; these contain the openings of sinuses which lead down to the diseased tissues in the deeper parts of the limb. From the sinuses an oily discharge is given off ; this contains small, rounded granules, which are made up chiefly of the fungus. The disease got its name of Madura foot from the frequency with which it occurs in the southern Indian

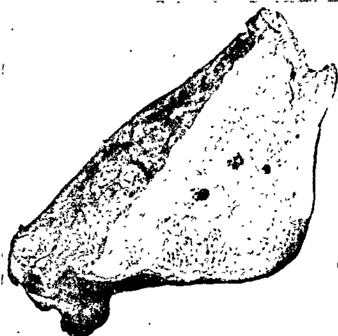


FIG. 62. Madura foot. (Wellcome Museum of Medical Science.)

district of that name, while mycetoma literally means a "fungus tumour." The disease was first clearly described by Vandyke Carter in India in 1860–74. It is widely distributed in scattered areas of India, the East Indies, China, North Africa and America, and cases have been reported from Eastern Europe, Somaliland and North Africa (*see* Fig. 62).

Ætiology and Pathology. Several kinds of mycetoma fungi have been described in various parts of the world, but clinically there are three chief types characterised by the discharge from the sinuses of white, black or red small round granules like the roe of fishes, and on section the affected tissues contain numerous granules of similar colours. The white variety is by far the most common, the black not very rare, but the red is very infrequently seen. The fungus consists

of a mycelial mass at the periphery of which the threads have terminal thickened ends. It invades all tissues, including the bones, and causes inflammatory swelling, followed by softening and breaking down of the structures of the limb, which becomes greatly enlarged and covered with nodules, which appear one by one. From the centre of each nodule a sinus leads down to the disorganised deep parts of the limb, from which the roe-like granules escape. The process is very chronic, the enlargement of the limb may be up to three times the normal size. There is very little tendency to heal, and death commonly takes place after ten to fifteen years.

Progress. The fungus which enters the body through some abrasion or through the prick of a thorn, spike of barley, etc., probably exists naturally as a saprophyte on plants. It usually enters through the sole of the foot, and a rounded painless swelling first results; this steadily extends over many years until the foot or hand becomes enlarged as new areas become involved, break down and form discharging sinuses. The bones become softened and disintegrated together with the other tissues, and the joints are destroyed, but the infection does not involve the glands and the internal organs; in these respects it differs from the related disease, actinomycosis. Secondary septic infections may occur, but the disease does not often kill directly, and the patients eventually die of some intercurrent affection.

The **diagnosis** is usually easy from the clinical appearances, and it may be confirmed by finding the fish-roe like granules in the discharge.

Treatment. Complete excision of the affected tissues in the early stage, or amputation of the affected limb above the part which is invaded by the fungus is the only reliable treatment. A case of black mycetoma tumour, of several inches in diameter, on the inner side of the foot, was seen in Calcutta, in which excision of the greater part of the growth, followed by X-ray treatment, was successful in curing the patient. In some forms of the disease large doses of potassium iodide or sodium iodide intravenously have been reported to be of value, as in actinomycosis, so this drug may be worthy of trial before resorting to the drastic but more reliable methods. No local applications can reach the widely disseminated fungus, so antiseptic dressings are only palliative in nature. Sulphadiazine in doses of 1·0 gm. every four hours during the day-time for three weeks is reported to have cured a case. Variable results have been recorded following the use of penicillin; it probably acts only on secondary infections.

BLASTOMYCOSIS

This term has been applied to a variety of skin diseases occurring in the tropics all over the world. It has been closely studied in Argentina where it is common. The condition is caused by a yeast-like organism of which A. Castellani and A. J. Chalmers describe four genera and numerous species.

Clinically, there is dermatitis with a warty condition, miliary abscesses, ulcers, sinuses, especially in the gluteal region or even myxomatous growths in the skin, which are sometimes very intractable. More rarely the oral and pharyngeal mucous membrane may be involved, and extensive ulceration may result, or hypertrophy of the filiform papillæ of the tongue producing the condition known as black tongue. Occasionally internal organs, such as the lungs and other viscera, may be invaded, with serious results, including fever and other symptoms simulating those of pulmonary tuberculosis. In such



FIG. 63. Blastomycosis of face. (M. G. Wohl.)

cases the prognosis is bad, but as long as the lesions are limited to the skin, recovery may be expected in time ; the disease may be very chronic, especially when gluteal or perineal sinuses are present. The diagnosis depends on finding the yeast-like fungi in the affected tissues (*see* Fig. 63).

Treatment. This requires much patience, as the only remedies known to ameliorate the condition are large doses of iodide of potassium or sodium such as 20–30 grains three times a day, and X-rays. When tumours are present 1 per cent. solutions of potassium iodide may be injected into them. Local and oral use of sulphathiazole may result in healing.

RHINOSPORIDIUM TUMOURS

These are small polypoid tumours of the mucous membrane of the nose and neighbouring parts, caused by a rhinosporidium parasite, most likely contracted while bathing. They are very common in India, but were first recognised in Argentina, and have also been met with in Siam, the East Indies, East and South Africa. They form small red rounded polypi, most frequently in the nasal cavities, but also affecting the conjunctiva and urethra, and they show small seed-like prominences on their surfaces, which on section and microscopical examination are found to consist of sporangium cysts containing very numerous small spores; the occurrence of these makes the condition very easy to recognise. Slow multiplication of the spores is said to have been



Fig. 64. Ainhum. (Col. Donovan.)

obtained by culture on Sabouraud's medium, and similar tumours are found in the nasal cavities of horses.

Treatment consists in removing the little polypi with a snare and destroying their bases with an electric cautery, and they are also said to disappear under tartar emetic or neostibosan given intravenously.

AINHUM

Ainhum is a peculiar disease of unknown causation, occurring in India and the East, and also in negroes of Africa and America, mainly in males of twenty to thirty years of age, in which a circular groove appears, most frequently at the base of one or both the little toes, less commonly on one of the other toes; it may go on to produce severance of the distal part without necessarily causing actual ulceration, with or without pain. It is rare in females; it runs a course of several years without causing other than trifling inconvenience. A case has

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opening; the inhabitants of the affected areas become expert at this process. The applications of antiseptics, such as a mercurial ointment or chloroform, will kill the insects, when they will be expelled by ulceration. Spraying each opening with about 2 c.c. of ethyl chloride on alternate days has been reported to cure within a week.

Keeping the floors of infected places clean and wearing boots are the simplest **prophylactic** measures; sprinkling the floors with pyrethrum powder, D.D.T., carbolised water or kerosene emulsion is recommended for destroying the fleas. Careful examination of the feet every day for the fleas, which look like black dots, is essential in the endemic areas.

LYMPHOGRANULOMA INGUINALE OR CLIMATIC BUBO

Definition. A disease, nearly always of venereal origin, and caused by an ultramicroscopical virus. Findlay, in 1938, described large and small forms of the virus indicating that a developmental cycle occurs. It commences with a small transitory herpetiform ulcer with associated lymphangitis of the inguinal glands or sometimes, in females, of the ano-rectal gland, with the formation of suppurative points, sterile as regards bacteria. The disease is later sometimes complicated by chronic elephantiasis, ulceration of the vulva or inflammatory stricture of the rectum.

Distribution. The disease has now been met with in every continent of the world, including the most important countries of Europe; a few cases have been seen among seamen in the East-London dock area. In the U.S.A. some 80 per cent. of the cases are in negroes; the disease is also prevalent in South America. In the Madras province of India it is common and is frequently complicated by other forms of venereal disease. It is not uncommon in the Dutch East Indies, China, Pacific Islands and the warm northern parts of Australia. C. C. Chesterman saw it in the Belgian Congo.

Ætiology. Recent work has thrown much light on the above-mentioned conditions through the proof by Hellerstrom and Wassen in Stockholm in 1930 (confirmed by Levaditi in Paris and Findlay in London), of a virus in the infected glands which could be communicated to mice and monkeys, and by the diagnostic value of Frei's intradermal test of 1927, by which a number of lesions previously described as separate entities have been shown to be due to the same cause. Minute Giemsa-staining particles may be found in cells of the affected glands, and Miyagawa has reported successful cultures on chorioallantoic membrane. The disease has most frequently been met with in males infected by low-class prostitutes. It is much commoner in men than in women because the infection lasts longer in the latter, one of whom may infect a number of males. Women who have infected males may show no definite signs of the disease except a positive Frei reaction. In America some infections have been ascribed to *coitus buccalis*.

Symptoms and Course. A few days after the infecting coitus a

been recorded in the United States in which a mother and her son aged three and a half years had both great toes affected. They healed in the winter, but became inflamed in the summer when the patients went barefooted.

No treatment is available other than amputation, which is needed when the distal end of the toe becomes so thickened as to be a nuisance (*see* Fig. 64).

CHIGGER DISEASE

The chigger is a flea, *Tunga penetrans*, the impregnated female of which burrows through the skin, usually of the feet. The insect grows to the size of a small pea ; the ova are discharged through an opening in the skin, and develop into adults in dry sand and dust and in the floors of insanitary huts. The disease was originally one of the West

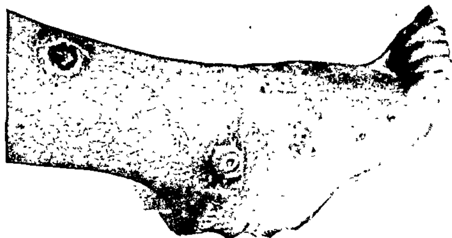


Fig. 65. Chigger disease. (By kind permission of Sir P. Manson-Bahr.)

Indies, but it has spread all over tropical Africa, and especially East Africa, and has been carried to India ; it is commonest on the sea coasts, as the insect is essentially a dweller in sand.

Symptoms. The irritation set up by the presence of the rapidly growing flea produces inflammation with the formation of pus, and the small pea-like swelling in the skin ulcerates. After all the eggs have escaped the insect is expelled, and the small remaining ulcer heals. Any number, from one to hundreds, may be present ; as a rule only a few are found at one time ; considerable incapacitation may be caused when the feet are extensively involved. As soon as the small ulcer has formed the posterior segments of the flea may be seen in the opening ; this allows the condition to be recognised (Fig. 65).

Treatment. If the flea is detected before it has burrowed through the skin it should be removed. Later, when the small tumour forms, the insect can be extracted with a needle after enlarging the small

CHAPTER XIX

ANCYLOSTOMIASIS

Definition. *Ancylostomiasis is a disease caused by the presence of* hookworms in the small bowel. These worms are the nematodes *Ancylostoma duodenale* and *Necator americanus*. The larvæ of the worms usually enter the body through the skin of the feet, which have come into contact with damp earth contaminated by infected fæces. The worms produce toxic effects and loss of blood. The symptoms of the disease are anæmia, debility, and digestive disturbances. Ancylostomiasis is a very common disease in many parts of the tropics ; it causes a vast amount of economic loss in a number of hot, damp countries, in which a large proportion of the population may be infected.

Historical. About a century ago Dubini noted hookworms in the upper small intestine in cases of anæmia, and in 1854 Griesinger attributed Egyptian chlorosis to their action. More widespread attention was directed to the disease when Perroncito, in 1879, reported cases of fatal anæmia, in which he found that some thousands of hookworms were present. These cases occurred among workers engaged in the construction of the St. Gothard tunnel, where the soil was hot and damp.

In 1878 Grassi pointed out the diagnostic significance of ancylostome eggs in the stools, and considerably later Looss, in Egypt, discovered that the larvæ which had developed in fæcally contaminated soil penetrated the skin of man and reached the bowel after a remarkable journey *viâ* the *blood stream, the air passages and the alimentary* canal. In 1902 Stiles described a second species, *Necator americanus*. This variety has been found in an African pigmy tribe so it may have been carried to America by Negro slaves. *A. duodenale* has been found in civet cats, tigers and the African gorilla ; young dogs and cats can be infected. The serious amount of debility and anæmia produced by these widely diffused nematode parasites is now generally recognised, but much difference of opinion persists as to whether light infections do or do not cause damage to the body.

Distribution and Prevalence. Warmth and moisture are necessary for the effective propagation of hookworm disease, so it is especially prevalent in tropical and sub-tropical countries, and also under such special conditions in colder regions in such places as the deep mines of Cornwall and Belgium, and in the St. Gothard Tunnel works, in which high temperature, soil moisture and bad sanitation occur. In American mines infections are most frequent when the temperature exceeds 25° C. ; they are common between 22°–25° C. and a few cases occur below those temperatures. Field-work infections are frequent in

small herpetiform ulcer of short duration appears, usually on the coronary sulcus in the male or the vulva in the female ; this is followed after one to three weeks by enlargement of the inguinal glands, sometimes accompanied by fever, with leucocytosis, which may be prolonged. One to several glands may be involved, and points of suppuration may develop in them containing pus sterile on culture, and the surrounding connective tissue may be involved with the formation of a large tumour, and occasionally a large single abscess may result. The iliac glands are also enlarged, but very rarely suppurate. The condition is essentially a specific inflammation of the lymph spaces and glands, accompanied by congestion, endarteritis obliterans and collections of macrophage epithelioid cells scattered through the glands. Elephantiasis of the lower limb may ultimately result from the lymphatic obstruction and fibrosis, especially if a mass of enlarged glands has been removed, but in milder cases subsidence may take place without serious permanent damage.

In women the inguinal glands may also be affected, but infection of the lymphatics tends to pass back to the ano-rectal glands between the vagina and the rectum and perineal regions ; this causes in some cases elephantiasis of the vulva and inflammatory stricture of the rectum 2–8 cm. above the anus.

Frei's intradermal test is of great diagnostic value. Positive reactions may be obtained about three weeks after the development of a bubo. It is carried out by means of an antigen consisting of sterile pus aspirated from an inguinal bubo, diluted in saline, and heated to 60° C. on two consecutive days and then kept at a low temperature. In positive cases an intracutaneous injection of 0·1 c.c. is followed by an inflammatory area at least ½ cm. in diameter, with a small central zone of necrosis after forty-eight hours. Emulsions of the brains of infected mice and monkeys can also be used as antigens in this test. Both *inguinal granuloma and climatic bubo, and also the later stage of rectal* stricture, give positive reactions.

Treatment. In non-suppurating cases surgical interference is to be avoided for fear of the later development of elephantiasis. If suppuration is already present incision with free drainage is necessary, and it may be well to dissect out individual suppurating glands with as little interference with the lymphatic system as possible. Sulphonamides in large doses have definite beneficial action. Penicillin is also effective. Aureomycin in 0·5 gm. doses given four times daily for four days has been reported to produce a cure. Frei's antigen has also been favourably reported on ; this consists of pus from infected glands, diluted 1 to 4 with saline, and sterilised by heating to 60° C. for one hour on three successive days, and used either with or without previous filtration, in doses of 0·2 c.c. gradually increased to 1·6 c.c. at two- to four-day intervals.

LEONARD ROGERS

Indies, Brazil, etc., hookworm infections are serious and cause much disability (*see* Fig. 66). *At Jaffa, in Palestine, Scott reported an increase* of ancylostomiasis as the result of summer irrigation with greatly increased larval infection of the soil.

The total disability in the world, due to this parasite, is thus very great but it is only in areas in which the climate is moist for a considerable part of the year that the more serious infections are common. The larval forms rapidly die out in soil which has become thoroughly dry, hence a period of prolonged dry weather destroys the infectivity of the soil.

Ætiology. The two varieties of hookworms differ only in their microscopical characters; both are frequently found together in the same patient, but the ancylostoma is larger than the necator. The latter can be distinguished most easily by having a projecting dorso-

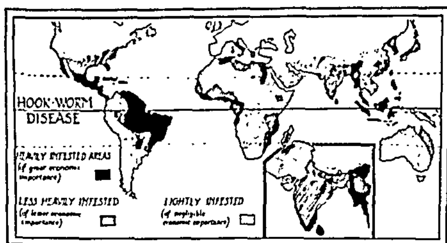


Fig. 66. Map of world and of India showing hookworm incidence.

median tooth in a smaller buccal cavity, but their differentiation is of little practical importance. The female worm measures about half-an-inch and the male one-third of an inch in length; the former has a pointed tail; the male has an expanded umbrella-like bursa with which it clasps the female; the male is much thinner than the female. A third rare variety, *Ancylostoma braziliense*, occurs commonly in dogs and cats in Brazil, and occasionally in man, chiefly in the Malay States, Siam and India, but it is of comparatively little importance, although in rare cases it has been found to invade the submucosa of the small bowel. It is considerably smaller than *A. duodenale*, and its internal pair of ventral teeth are very much smaller. *A. duodenale* weighs twice as much as *N. americanus*, so is probably about twice as harmful.

The hookworms are found attached to the mucous membrane of the small intestine, mainly in the jejunum and the lower part of the duodenum; they may number up to 1,000 to 4,000 in severely infected

subjects of ten to twenty years of age. The lower incidence at higher ages may be due to partial immunity ; this has been induced in dogs by repeated experimental infections. The extensive hookworm campaigns of the Rockefeller Foundation in many parts of the world have thrown much light both on the percentages of people who are infested and the degrees of their infestation. The great practical importance of the latter factor became evident when it was found in the West Indies and British Guiana that a year or more after treatment two-thirds of the patients might have become re-infected, yet the great improvement in their health persisted. The explanation is that the number of worms present in each person was far less than before treatment. In later campaigns modern methods of estimating the degree of infection have been employed ; these take the form of counting the ova in measured amounts of the patient's stools (*see* p. 375). In this way the degree as well as the percentage of infections is ascertained and valuable evidence has thus been accumulated.

In the Western Hemisphere the most serious infections occur in the tropical zone where high temperature and heavy rainfall co-exist. The southern United States, the West Indian Islands, and the north of South America as far south as Brazil and the northern portions of Argentina, are places in which a serious amount of disability is caused. In some areas the average number of worms in each person is 100 or more, and many times that number may occur in the most highly infected patients. In West Africa smaller percentages of the population are affected and the average infection is very light, but the number of reported observations is too small to allow of safe deductions being made as yet. R. M. Gordon, in this area, classified his cases in accordance with the egg counts, but found neither anæmia nor loss of physical or mental energy in persons with the lower degrees of infection. In the dry portions of South-east Asia infections are few, and Chandler found that the infections were very light in the dry north-west parts of India, and the effect of these on the health of the people was "everywhere practically negligible." In the sub-Himalayan division of Northern India, from the United Provinces to Assam, the incidence *increases from west to east with the increasing rainfall* and humidity, and reaches its maximum in very humid Assam, which has six months or more of rain, but with the exception of Assam, Burma and Malabar, Chandler found that the average number of worms was rather low, and the amount of disease produced was not serious. Extensive observations of Mhaskar, in the Madras Presidency, also showed a high percentage of light infections with an average count of only ten worms ; he found this number to be compatible with good health. These findings show the necessity of working out the degree as well as the percentage of infections, for those who harbour a very small number of worms do not appear to suffer any harm. In the very hot, humid climates of Ceylon, the East Indian and Oceanic Islands, the West

vesicles, and passing up the bronchi and trachea, escape into the œsophagus, from which they are carried down to the stomach, and on into the intestine, where they attach themselves to the mucosa and grow to maturity. In experimental infections eggs may still be found in the stools after eight or nine months.

Pathogenicity. B. K. Ashford, and many other authorities, hold that ancylostomes produce their effects on the system chiefly through

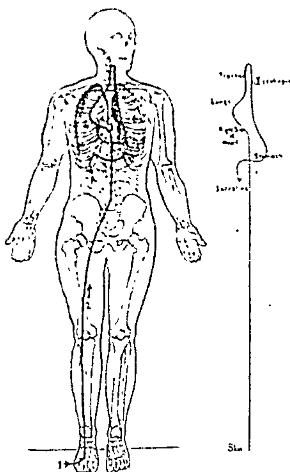


Fig. 67. Diagram of passage of hookworms from the skin to the duodenum. (Wellcome Museum of Medical Science.)

the action of toxins secreted by them ; the anæmia is regarded as being mainly due to a hæmolytic agent thus formed. Loss of blood resulting from the small hæmorrhages produced by the bites on the intestinal mucous membrane also plays a part, and so may inflammation and absorption of intestinal toxins through the minute wounds produced by the worms. The presence of eosinophilia is evidence of the action of a toxin, as is the case in many other helminthic infections. In healthy persons about 500 worms are required to cause definite symptoms of ancylostomiasis, but in debilitated subjects 100 or so may

cases. The females are usually filled with red or black altered blood, and petechial hæmorrhage spots are commonly seen at the point of attachment to the mucous membrane, or at the sites of recent bites. Occasionally an ancylostome may be found embedded in the intestinal wall at the site of a hæmorrhagic patch. The duration of the life of the worms in the human bowel was long in doubt, but observations in India by Mhaskar in Madras and Chandler in Bengal have shown that a rapid decrease takes place in the number of infected prisoners who are living under conditions in which fresh infections cannot occur. The latter worker found by means of egg counts that the reduction amounted to 50, 70 and 80 per cent. respectively after three, twelve and twenty-four months' imprisonment, and 93 per cent. at the end of six years. Kenrick infected volunteer prisoners with hookworm larvæ, and found that the ova first appeared in the stools after an average of fifty-three days, to reach their maximum in twelve to eighteen months, after which they declined by 50 to 70 per cent. during the next three to six months, and disappeared in an average of seventy-six months.

Ova are passed in the stools of infected persons in enormous numbers; different observers have estimated that one worm is present in the body for every 20, 44 or 100 eggs per gm. of stool.

The ova of both species of hookworm show similar characters; they are ovoid in shape, with a thin, unstained capsule separated by a clear space from a central mass composed of four to eight or more segments. Large numbers of segments are not seen in fresh stools, but they are common in stools which have been kept for some time. The eggs measure about 60 μ in length by 40 μ in width (*see* Figs. 84 and 85 of Coloured Plate).

Under favourable conditions of temperature and moisture, and in the presence of oxygen, the eggs soon develop into rhabditiform larvæ; the most favourable temperature is approximately 27° C., and the limits are 14°–27° C., according to Stitt. On reaching a length of about 300 μ by the third day they moult and an œsophagus appears; by the fifth day a second covering is formed; this remains as a protecting sheath for some time; the larvæ now measure 550 μ by 23 μ; they can survive with the help of moisture and shade for one or two months in this stage, especially on light sandy soil and are ready to penetrate the skin of any human being who walks barefooted over soil which harbours them (*see* Fig. 67).

Looss, in Egypt, discovered their mode of entry by accident. He spilled a culture of the young worms on his hand and soon noticed a smarting sensation; he actually saw the parasites penetrate his skin within a few minutes, and found that he developed hookworm infection in due course. He also traced their travels through the bodies of experimental animals and found that they reached the gut by the following roundabout way. The larvæ penetrate the skin, enter the veins and are carried to the lungs; here they escape into the air

cent.; when there are less than 300 worms it does not usually fall below 80 per cent., unless other causes of anæmia are also operating. The coagulability of the blood may be reduced in severe cases; when this occurs there is an increased loss of blood from the damaged intestinal mucosa. The sedimentation rate of the red corpuscles is reported to be greatly increased, a return to the normal indicates cure.

Do Very Small Numbers of Ancylostomes exert any Serious Deleterious Effects in Man?

There is still a great difference of opinion regarding the correct answer to this simple question. At first sight it seems difficult to understand how one to ten or even twenty of these minute worms can harm an adult who is in otherwise good health, especially as it is known that a child may withstand for months the presence of over 1,000 hookworms without fatal results. Yet experienced authorities, such as Stiles and C. A. Lane, hold the contrary view, and Ashford mentions that in innumerable instances only a few worms have caused tremendous falls of hæmoglobin. This he attributes to circulating toxins of the parasites, but here the fallacy that many worms drop off when the patient becomes very anæmic has to be guarded against. Moreover, in the most affected provinces of India, such as Assam, the treatment of jail inmates by anthelmintics has been followed by definite or striking improvement in their general health, due to the removal of a variety of worms, including ancylostomes.

On the other hand, their great practical experience, during several years' investigations in the endemic areas under the Rockefeller Foundation, has led W. G. Smillie and D. L. Augustine to the conclusion that the average number of worms present is of far greater importance than the percentage of the population which harbours one or more ancylostomes; they believe that "the greater proportion of persons with hookworm infestations of slight degree suffer no measureable harm, and should be considered, not cases of disease, but carriers." By the use of egg-counting methods, described later, they classified their cases as follows: (1) Very light infections, 1 to 25 worms; (2) light infections, 26 to 100; (3) moderate infections, 101 to 500; (4) heavy infections, 501 to 1,000; and (5) very heavy infections with 1,001 to 3,000, and they advise treatment in all infections from "moderate," upwards, but consider it unfair to subject persons with harmless light infections to drastic treatment. It should, however, be remembered that when, say, 50 to 100 hookworms are present in a patient weakened by malaria, dysentery or other debilitating disease, such a comparatively slight infection may be a factor in producing ill-health and require to be treated, as L. Rogers pointed out as long ago as 1898. Such authorities as Chandler and Mhaskar, in India, agree that it is unnecessary to give mass treatments to communities among whom light infections very greatly predominate over moderately

suffice. *Small hæmorrhages may be produced in the lungs by the passage of the embryos through them.*

In fatal cases the body is anæmic but well nourished, and often œdematous ; the heart is dilated and may be hypertrophied ; the liver shows fatty changes, together with excess of hæmatoidin pigment, and the kidneys show similar changes. A variable number of ancylostomes will be found attached to the mucous membrane, and small petechial hæmorrhages are often visible. In cases of long duration the number of worms is often comparatively small owing to the fact that many of the worms may drop off as the anæmia progresses, so that the number found post-mortem is no criterion of the number which were present at an earlier period of the infection. Ashford has recorded changes in the bone marrow and in the retroperitoneal glands similar to those of pernicious anæmia, and Stitt has met with a terminal pernicious type of anæmia in three cases.

Blood Changes. Hookworm anæmia is of the microcytic-hypochromic type which yields to iron treatment. In the absence of deficiency of iron in the diet hookworms even when numerous may produce no anæmia. The bone marrow shows very numerous normoblasts. *The characteristic feature of the anæmia is the much greater reduction in the hæmoglobin percentage than in the number of the red corpuscles, so that the colour index averages only about 0·5 instead of 1·0.* Thus, when the red corpuscles have fallen to 2,500,000 to 3,000,000, the hæmoglobin is reduced to about 30 per cent. or less. If the hæmoglobin is reduced to 15 per cent. the condition of the patient becomes serious. There is an increase in the volume of the blood and a reduction in the colour index in ancylostomiasis as in chlorotic anæmia, and Ashford attributed to the increased volume of the blood the power of patients to do some work when they have only 20 per cent. of the normal hæmoglobin. In severe cases the red corpuscles become irregular in shape and size and show polychromatophilic changes ; nucleated red corpuscles are also present. After the removal of the worms by treatment the red corpuscles increase more rapidly than the hæmoglobin, and so the low colour index persists for some time. The progress towards recovery must, therefore, be estimated by the hæmoglobin increase rather than by the red cell count.

Another important blood change is the presence of a considerable increase in the number of the eosinophile corpuscles, which commonly number from 10 to 20 per cent. of the total. This eosinophile increase is associated with a corresponding diminution of the proportion of the polymorphonuclears. In chronic cases the eosinophile increase tends to become less evident.

The degree of anæmia increases with the severity of the infection, but this relationship is not an absolute one. Thus, Ashford found that, broadly speaking, 1,000 worms are required to bring the hæmoglobin down to 40 per cent., and up to 2,000 worms to reduce it to 20 per

J. L. Korby-Smith to be to freeze round the visible end of the burrow for two to four minutes with ethyl chloride.

In light infections the early symptoms of the presence of the adult worms in the bowel are mainly those of digestive disturbances in the form of epigastric pain or tenderness, acidity, flatulence and loss of appetite ; these symptoms should lead to an examination of the stools for the ova if the patient has lived in affected areas, especially if they are accompanied by loss of energy, palpitation and breathlessness on exertion ; these are indications of the existence of a moderate degree of anæmia.

When **moderate degrees of infection** are reached the above symptoms will be *exaggerated and there may also be nausea and vomiting*, excessive appetite, with perversion of taste, leading to eating of earth, *intestinal fermentation with abdominal distension and constipation*, sometimes alternating with diarrhœa. There will now be obvious pallor with *dizziness, palpitation and breathlessness on slight exertion*, hæmic murmurs, great feebleness of body and mind, amenorrhœa or abortion in women, cessation of growth and mental deterioration in children, and pains or actual neuritis with diminished reflexes. Examination of the blood will now reveal very definite evidence of anæmia, together with an increase of the eosinophiles, which points to helminthic infestation as the probable cause of the anæmia.

In the advanced stage of **heavy infections** extreme debility occurs with general œdema of the face, scrotum and extremities, combined with a severe degree of anæmia. The symptoms and signs which have just been described are present to a still greater degree ; these, with the protuberant abdomen and evidence of dilatation of the heart, form a characteristic picture of neglected and dangerous ancylostomiasis. The hæmoglobin may now have fallen to 20 per cent. or less, and the colour index is low, except in the very rare cases in which there is a terminal pernicious type of anæmia.

Acute Cases Due to Mass Infection. In Porto Rico Ashford met with *six* acute infections due to *sea-bathing near an infected stream* ; these were characterised by ground-itch preventing sleep at night, weakness, *anæmia, diarrhœa, slight fever and eosinophilia, all developing* within a few weeks.

The complications, which are most common in advanced cases, include terminal acute diarrhœa, occasionally with hæmorrhage, or even dysentery, hydrothorax, or œdema of the lungs, syncope from dilatation of the previously hypertrophied heart, the pernicious type of anæmia, albuminuria without casts as a rule, melancholia, dementia or hystero-epilepsy, night blindness, dilatation of the retinal veins or retinal hæmorrhages, cataract in adolescents, and intercurrent diseases in general due to the enfeebled state of the patients, one of which may be the ultimate cause of death. It must be remembered that the great majority of cases of hookworm disease do not show any very striking

severe ones; such a state of affairs exists in most parts of India, as shown by these workers. Darling estimated that 10 to 11 worms in adults and 7·6 in children cause a loss of 1 per cent. of hæmoglobin, so light infections may produce no anæmia, as compensation is established. F. Fülleborn has reported that among the well-fed and malaria-free people of North Argentina the heavy average infection with 430 *N. americanus* produced far less clinical harm than did much lighter infections in unhealthy parts of Brazil. The harmfulness of any given number of worms will be increased by a diet deficient in iron.

Clinical Description

The clinical manifestations of ancylostomiasis vary widely according to the heaviness and duration of the infection. In addition there are many people in whom the worms are so few that no symptoms are produced. There is a certain amount of soil pollution by these persons;



Fig. 68. Skin lesions of site of entry of hookworms. (Dr. Baro.)

so they *may be a danger to a community living in primitive* sanitary conditions. The local dermatitis which occurs at the site of entry of the larvæ must also be borne in mind.

Ground or water itch is a dermatitis produced at the site of entry of the ancylostome larvæ; this usually occurs about the toes and on the inner sides or dorsum of the feet, as these are the sites where the larvæ naturally gain access to persons who walk barefooted on fæcally contaminated soil. The lesions consist of very irritable vesicles on an inflamed and œdematous skin. Ashford obtained a history of such a commencement of the disease in no less than 96 per cent. of many thousand cases, and it has also been described by C. A. Bentley, as being common among tea-estate coolies in Assam. F. Fülleborn produced such an eruption on his own arm thirteen days after the application of *mature larvæ of the dog-hookworm to a* scarified surface, and he traced the superficial wanderings of the larvæ just under the horny layers of epithelium by means of serial sections of removed portions of the affected skin (*see* Fig. 68). The most useful treatment for destroying the larvæ in creeping eruption of the skin was found by

one part of fæces with five parts of a salt solution with a specific gravity of 1·130. The eggs are collected by placing a glass slide for a few minutes in contact with the upper surface of the fluid. He obtained more positive results from the examination of two such slides than by either smear or centrifuge methods.

Quantitative estimations may be made most simply by Stoll's egg counting method. In this 3 gm. of fæces are diluted to 45 c.c. with decinormal sodium hydrate solution, and well shaken up with ten 3-mm. glass beads in a rubber-corked large test-tube to distribute the eggs uniformly throughout the fluid. Exactly 0·15 c.c. of the fluid is placed at once on a slide and covered by a slip measuring 22 by 40 mm. The number of eggs in the preparation multiplied by 100 gives the number of eggs per gm. of fæces.

Direct centrifugal flotation is claimed by C. A. Lane to detect the ova of a single intestinal female ancylostome. It necessitates the use of a special instrument by means of which all the ova in 0·5 c.c. of a stool are collected on 2 square inches of a slide fixed over the centrifugal tube containing the mixture of fæces and brine. The accuracy of this plan, if several spins of the centrifuge are made, has been confirmed in the field, and, although it takes more time than Stoll's plan, it is valuable to those who consider it necessary to remove the last ancylostome of patients.

Cultures of Ancylostomes. When ova are very scanty in the stools the addition of charcoal or agar, or both, to a portion of fæces, and incubation at 115° F. for a few days results in the development of active larval forms, which will collect in warm water added to the surface. The larvæ can be seen with the naked eye, but are best detected with the microscope. Baermann's apparatus also enables the larvæ to be found, and their movements in soil to be studied. By this means it has been found that the larvæ migrate only a few inches laterally from the place of deposit of infected fæces, but they can travel vertically to the surface from a depth of 2 or 3 feet through loose soil. The infected soil is placed in a coarse cloth in a sieve with 1 mm. mesh ; this is placed in a funnel containing water in which the larvæ collect. The water is drawn off for examination through a clamped rubber tube which is attached to the funnel. For diagnostic purposes the direct smear examination method and the flotation method are quite sufficient.

Prognosis. This is very favourable if the infection is discovered in good time and properly treated, and an immense saving in both life and labour, as well as improvement in health, has been effected by hookworm treatment campaigns in many warm countries in the last few decades. In very advanced cases it may be too late to save the patient's life by removing the remaining hookworms. In Ashford's experience the fewer the eosinophiles the worse the outlook, as a low eosinophile count indicates exhaustion of the blood-forming organs. The reduction of the hæmoglobin to under 20 per cent, indicates a

manifestations, so the disease should be suspected when there is evidence of insidious failure of health with anæmia, even if no special indications of the disease exist.

Diagnosis. The ultimate diagnosis can only be made by finding the ancylostomes or their ova in the stools, but the following are the conditions most likely to be confused with the disease. Beri-beri in its dropsical cardiac form may simulate the late stage of the helminthic infection, but the history of onset will usually be more acute and nerve symptoms will predominate. In acute or chronic Bright's disease the œdema closely resembles that of advanced ancylostomiasis, but in the latter the degree of anæmia will be greater, the blood pressure will be low and casts will be rare or absent. The usual indications of nephritis are rarely pronounced in hookworm disease. Pernicious anæmia has a high colour index, characteristic changes in the red cells are present, eosinophilia is not a feature of the disease, and œdema is present only in very obvious cases. Malaria has a fairly high colour index, as has the anæmia of kala-azar, and the presence of the respective parasites of these diseases will complete the differentiation, while the spleen is not enlarged in a pure helminthic infection. It must be remembered that many patients who are infested with hookworms also have malaria or other diseases, and also that a person in whose stools the ova are found may be suffering from anæmia, due to a very different cause. In other words, the finding of the ova does not justify us in assuming that we have completed the diagnosis.

Methods of Finding and Estimating the Ova in the Stools. The recognition of advanced stages of ancylostomiasis presents few difficulties to the practitioner who is familiar with the disease in its endemic areas, but the detection and cure of the early stages, so as to prevent the development of obvious clinical signs, is far more difficult as well as of greater practical importance ; it can best be effected by a search for the characteristic ova in the patients' stools by one of the following methods.

In most cases of severe hookworm infection the eggs can be found by examining a moist preparation made by mixing a little fæcal material with water or normal saline, but slighter infections may easily be overlooked, and numerous methods of concentrating the ova have been devised, of which the following are the simplest and most reliable.

Barber's flotation method consists in mixing well on a slide a small portion of fæces with equal parts of glycerine and a saturated solution of common salt, and allowing the solid particles to settle, when with the microscope the ova will be found floating on the top of the brine mixture, whose specific gravity is greater than that of the eggs. In using this method Mhaskar advises passing the diluted stool through wire gauze of forty meshes to the inch, and allowing it to stand for thirty minutes after adding 5 per cent. of saturated gum solution, to prevent evaporation. H. H. Willis mixes thoroughly in a tall container

Carbon tetrachloride is one of the more reliable drugs ; it has the advantages of simplicity of administration and great cheapness, while, if it is pure and is not administered in too large a dose, it has a great degree of safety, although neglect of proper precautions has led to some accidents. Its value was first noted in the treatment of dogs by M. C. Hall in 1921, long after the above-described drugs had become established in use, and it replaced them to a considerable extent in field work, but should be avoided in persons suffering from diseases of the liver, kidney or heart, and also in the case of alcoholics. It cannot be regarded as an absolutely safe drug for indiscriminate use in mass treatment. Its cost is only about ⅛*d.* for each case ; much less than the cost of thymol. It has the further advantage that a preliminary purge is unnecessary, and that it can be given in a mixture which contains the purge in the same dose, so that an after-purge is not absolutely necessary, but, on the other hand, it is not so effective against round and other worms. It should be kept in a cool dark place, for on exposure to light phosgene gas, which is irritant to the lungs, may be formed in it.

Dosage. The pure drug, free from carbon bisulphide, can be given in 3 c.c. doses, and in children 2–3 minims may be given for each year of age ; best administered in hard gelatine capsules in the early morning after twelve to eighteen hours' fasting. A. C. Chandler advises a saline purge after the drug, and a diet rich in carbohydrates to lessen possible action on the liver. Very large numbers of cases have been treated successfully with this drug in Egypt, Fiji, India and other places, but although many thousands of persons have been treated without accident, every now and then there have been unexplained fatalities.

In 1928 Lambert reported that 3,000,000 carbon tetrachloride treatments in Fiji prevented the former rapid re-infections, with the result that the disease was controlled and eliminated as an economic factor. Ten years later Lambert found through a survey only half the previous number of infections, and those in a less severe form with few clinical signs of hookworm disease, where formerly there had been almost universal anæmia. Improved sanitation and systematic treatment of cases had helped to obviate the need for further mass treatments. Very similar results are reported from Nauru Island by A. M. B. Grant, where an ancylostome infection rate of 89 per cent. was reduced to 1 in 700 persons examined.

Oil of chenopodium and carbon tetrachloride can be given together in doses of each that are below the dangerously toxic ones ; a further advantage of this combination is that the mixture acts on both hookworms and round worms. Thus, Pessoa advises 1·5 c.c. of carbon tetrachloride with 0·75 c.c. of ascaridol in adults in a single dose followed by a saline purge after half an hour. This method effected the removal of 98·9 per cent. of the worms. H. R. O'Brien, in Siam,

dangerous condition, and the onset of the pernicious type of anæmia is also of serious prognostic import; fortunately, this is a very uncommon condition. The complication of pregnancy by hookworm infection, usually accompanied by œdema and albuminuria, is of serious import.

Treatment

The treatment of hookworm cases under careful control is very satisfactory. Several drugs are used, but some of them are toxic to the human system. Cost has also to be taken into account, owing to the immense number of patients in some areas. The following are the most useful remedies :—

Thymol is one of the oldest and safest of anthelmintics, but is now rarely used on a large scale on account of its high cost, disagreeable taste and the necessity for giving a saline purge both the evening before and two hours after the morning administration of three doses of 20 grains each at hourly intervals, followed by rest for a day. As the drug is soluble in alcohol, turpentine, chloroform or oils, including castor oil, these must be avoided during the treatment. The total dose of 60 grains is given to persons of twenty to sixty years of age. The total dose should be 7½ grains for children under five, 15 grains at five to ten years, 30 grains at ten to fourteen years, and 45 grains at fifteen to twenty and over sixty years of age. Some 90 per cent. of the worms are removed at one treatment, which may have to be repeated if ova are present in the stools after a week. In pregnancy the dose should not exceed 20 grains.

Oil of chenopodium, and its active principle, **ascaridol,** are very efficient anthelmintics against hookworms, round worms, and other helminths, but the whole oil has the disadvantage that different samples contain varying amounts of the active principle, ranging from 40 to 65 per cent. Fatal results have followed the administration of certain doses of strong fresh samples, whereas similar doses of weaker samples had previously been harmless. For this reason it is essential to know the ascaridol content of any new stock of the oil, or only to use the pure ascaridol. As its cost is one-fifth of that of thymol, it has been largely used in hookworm campaigns, especially before the discovery of carbon tetrachloride and tetrachlorethylene. It is now generally acknowledged that the total dose should not exceed 1·5 c.c. of the oil of chenopodium. It is best given in three doses of 0·5 c.c. (8 minims) each in gelatin capsules at hourly intervals early in the morning after an over-night saline purge; it should be followed an hour after the last dose by a second saline purge, and the patient should rest for the remainder of the day. From 90 to 99 per cent. of the worms are removed by this dosage, which may be repeated after a week or ten days if hookworm ova are still present in the stools. The doses for children should be in proportion to the body-weight.

destroy ancylostoma ova. The same result would be obtained by the universal wearing of boots by which the access of the larvæ to the skin of the feet would be made much more difficult. Unfortunately, the affected populations are often too poor to afford boots, and the enforcement of effective sanitary measures is very difficult even in the case of the labour forces under European control, for example, on tea estates. Chandler, as the result of very extensive investigations in India, points out that European types of pail-latrines are unsuitable for tropical indigenous labour on account of their rapid fouling, and he recommends the use of more primitive methods which have proved practical in some places in India, such as squatting on bamboos placed six inches above the ground over pits or drainage channels. In Southern India, experiments are being made with latrines consisting of deep holes bored in the ground by a special machine, and the results are said to be promising. Trench or pit latrines should be at least three feet deep, otherwise the larvæ are able to work their way to the surface of the soil in the immediate neighbourhood. When latrines of the orthodox type are used it is essential that it should be easier for the people to use them than to defæcate promiscuously on the soil, and it is important that the latrines should be covered so as to keep the floor dry and also to promote the comfort of the users. The conditions are so varied that it is impossible to lay down rules which are of universal applicability, but a knowledge of the habits of the hookworm and of the method by which the infection is spread will afford a reliable guide to those who have to deal with the problem of prevention.

Salt, spread over contaminated soil in sufficient quantities to form brine, will prevent the development of the larvæ in mines or other contaminated ground, and is a useful measure under some conditions. Covering the floors of latrines and stools with common salt to a thickness of $\frac{1}{4}$ to $\frac{1}{2}$ of an inch prevents the development of hookworm larvæ, and weekly washing of latrines with a 20–30 per cent. salt solution is also a valuable prophylactic measure. Chandler believes that, if re-infections could be prevented by such methods, all but the worst infections would become automatically reduced to harmless proportions within a year, for he has shown that in the very extensive areas of India, with only about four months' rainy season favourable to the spread of hookworm infection, there is usually a high percentage of very slight degrees of infestation, but very few of a harmful kind.

Treatment campaigns are essential in the more heavily infected areas. Darling advises that where the average hookworm infestation is high enough to cause serious disease and economic loss, some 90 per cent. of the population are likely to be infected, and mass treatment should be carried out ; under these conditions examination of all the population for infection is an unnecessary waste of time and funds. Even where re-infection cannot be entirely prevented owing to lack of efficient sanitation, it has been found by the Rockefeller workers that

treated 250,000 persons with a maximum dose of 2 c.c. of a mixture containing 40 per cent. of oil of chenopodium and 60 per cent. of carbon tetrachloride without a single death due to the drugs. In children under fifteen years two drops for each year were given in castor oil, and in adults the dose was given in two parts at an hour's interval in the morning, followed by a saline purge an hour after the second half-dose. Chandler and others have used this plan with success in India.

It is of the utmost importance that the drugs used should be of a high degree of purity, that the dosage should be accurate and should be in proportion to the body-weight. It is recommended that a careful inspection should be made of the persons who are to be treated and that they should be under proper control on the treatment day. The stage has not yet been reached when 100 per cent. safety and 100 per cent. efficiency can be claimed for any line of treatment.

Tetrachlorethylene has been found to be of great value in hookworm infections. In Calcutta P. A. Maplestone reported it to be easy to administer, cheap, efficient and even safer than thymol. He advised a 4 c.c. dose mixed with 2 oz. of saturated magnesium sulphate, to which 1 c.c. of oil of chenopodium might be added and the whole well shaken in a bottle to form a fine emulsion. Two treatments effected complete or practically complete cures in 87 per cent., and three treatments cured all the patients who returned regularly for treatment and subsequent examination. In Brazil a single 4 c.c. dose of tetrachlorethylene in a gelatine capsule is reported to have removed 95 per cent. of Necator ancylostomes, so this drug seems likely to replace the more toxic carbon tetrachloride.

Hexylresorcinol has been recommended for mass treatment in rural districts in doses of from 0·4 gm. in children under five years of age to 0·9 gm. for those over thirteen given in capsules. The dose may be repeated after twenty days. It is also effective against ascaris.

General Treatment. In severe cases of hookworm disease, after removal of the worms 10–20 grains of ferrous sulphate daily will materially assist recovery from the anæmia. In cases with œdema vitamin B in the form of brewer's yeast, betaxin, or marmite has been reported to be of value. In cases showing a dangerous degree of anæmia L. E. Napier and others have found it safer to give a course of iron before attempting the removal of the worms by drastic anthelmintics.

Prophylaxis. The prevention of hookworm disease is as simple in theory as it is difficult in practice among the indigenous people of the endemic areas. The obstacles are due to the extremely primitive sanitary habits and the poverty of the communities concerned. Now that it is known that under proper sanitary conditions in Indian jails the inmates rapidly lose their infections, it is clear that the proper disposal of fæcal matter will reduce the infection to harmless proportions. Both septic tanks and Chinese sewage-tank storage of night soil

CHAPTER XX

FILARIASIS

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FILARIASIS DUE TO W. BANCROFTI

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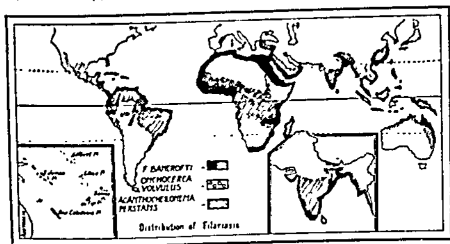


Fig. 69. Map showing world distribution of filariasis.

In 1876 Bancroft, in Australia, discovered the adult worm.

In 1878 Manson traced the development of the embryos in the mosquito intermediate host *Culex fatigans* ; shortly afterwards he described the nocturnal periodicity of the embryos in the human blood.

In 1900, when cutting sections of infected mosquitoes sent by Bancroft to Manson, G. C. Low observed that the developed forms of the embryos escape from the proboscis of the mosquito during the act of biting, and so must penetrate the skin of the human host in whom they complete their life cycle ; S. P. James, in India, independently came to the same conclusion at about the same time.

Geographical Distribution and Prevalence. This parasitic worm is very widely distributed throughout the tropical and sub-tropical zones of both the new and the old world. It is especially common in some

at the end of a year or two the new infections will be of a much lighter grade than those which existed before treatment, and the health of the community will remain much better than before the measures were undertaken. The campaigns have therefore been of great value, in spite of the fact that the results obtained have fallen short of the ideal of removing every worm and preventing re-infections from taking place. The greatest good of the greatest number will therefore be attained by the removal of all serious and harmful infections by carrying out mass treatment at intervals over as wide an area of country as possible without spending unnecessary time and labour in aiming at the theoretical ideal of removing the last worm from the people of a smaller portion of the immense tracts which still require attention. The Rockefeller Foundation results are confirmed by the experience of similar measures in Fiji and Nauru Island already mentioned.

LEONARD ROGERS

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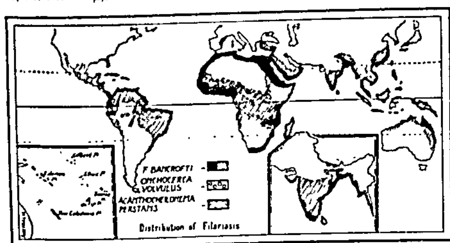


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of the West Indian Islands such as Barbados and in British Guiana, in low-lying deltaic areas in the East Indies, on the east coast of India and Travancore, in Ceylon, in Central and Southern China, in the coastal area of Queensland, and on many of the Oceanic Islands, in some of which Manson-Bahr found 60 per cent. of the people to be infected. It occurs throughout tropical and North Africa down to the Anglo-Egyptian Sudan, with very high recorded rates of infestation in Nigeria and Tanganyika, and in America from the Southern United States to Argentina (Figs. 69 and 70).

The incidence varies greatly even in neighbouring localities, so that very high prevalence in certain areas may occur without a high incidence in the country as a whole. In India, for example, the endemic areas of filariasis are limited, although the disease constitutes a serious cause of disability in the affected places. The endemicity is closely related to the presence of numerous mosquito carriers, and to the existence of hot, moist atmospheric conditions which appear to be essential for the spread of infection.

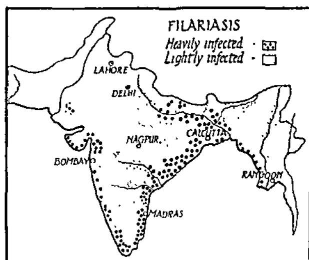


FIG. 70. Map of India showing distribution of filariasis.

The age distribution shows an increasing rate of prevalence after twenty years, and the sex incidence as a rule shows higher rates in males. The racial prevalence probably depends on the liability to infection through living in close relation to infected persons, as all races appear to be equally susceptible.

Ætiology. The adult *W. bancrofti* is a long thread-like worm, the male measuring 40 and the female 90 mm. in length by 0·1 and 0·28 mm. in breadth respectively. The worms are thus easily visible to the naked eye, and when found encysted in thin-walled sacs of dilated lymphatics they are extremely active in their movements, but die within a few hours of being removed from the human body. They inhabit the lymphatic vessels of the abdominal cavity in particular, and may be found from the thoracic duct down to the lymphatics of the lower extremities, especially those of the groins ; several may occur in a bunch. They may also be present in the lymphatic vessels in any part of the body ; common sites are elephantoid tissues of the external genitals, mammary glands or the extremities, abdominal retroperitoneal lymphatics, including those of the kidneys and the epididymis. The worms are so slender that they are very difficult to find in the tissues

after death, and when present in abscesses they are often dead and undergoing decomposition.

The embryos of *W. bancrofti*, called *Microfilaria bancrofti*, are far more familiar objects than the adult worms, for as long as the latter live in lymphatics communicating directly with the blood stream the microfilariæ are present in large numbers in the peripheral blood, where they continue to appear for years. They are about 300 μ in length and 7·5 to 10 μ in breadth, so they can pass through capillary vessels; they possess a thin sheath, which is best seen where it projects slightly beyond the extremities of the embryo. The numbers of microfilariæ may be so great that several hundred may sometimes be counted in 20 c.mm. of the finger-blood taken in the evening, so that many millions may be present in the circulation at one time, and that too in persons in perfect health (Fig. 71).

The periodicity of the microfilariæ first described by Manson consists

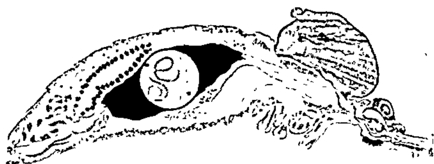


FIG. 71. Diagram of filarial development in mosquito. (Wellcome Museum of Medical Science.)

in the complete, or nearly complete, absence of the embryos from the peripheral blood during the daytime up to about 6 p.m., after which they steadily increase and reach their maximum numbers about midnight; they then decline rapidly, to reach their minimum about 9 a.m. It is significant that the most frequent intermediate host, *Culex fatigans*, bites chiefly at night, when it has the greatest chance of becoming infected with the parasite. A remarkable fact is that P. Manson-Bahr found in the Pacific a very similar filaria whose embryos are non-periodic and so are present in the peripheral blood by day, and these are conveyed by a mosquito which bites in the day-time, *Aëdes variegatus*, and O'Connor has found that the range of this filaria coincides with that of its mosquito carrier. In view of this interesting fact it is useless to discuss the numerous ingenious theories propounded from time to time to account for the periodicity of *W. bancrofti*, as none of them can explain the absence of periodicity in the Pacific species. The periodicity of the embryos can be reversed by making the patient sleep during the day and keep awake at night.

Numerous species of mosquitoes serve for the development of microfilaria sucked up in the blood of infected persons. They include *Culex fatigans* in India, *Culex pipiens* in China, varieties of *Aëdes* in the Pacific Islands and Japan, *Mansonioides* in Africa and *Anopheles* of West Africa and India. The last named is not readily killed by surface oiling.

The development of the parasite in the mosquito takes place in the thoracic muscles, which are penetrated within twenty-four hours by the microfilariæ after first discarding their sheaths in the stomach of the mosquito, aided apparently by the increased viscosity which occurs in the blood after being swallowed by the insect (Fig. 71). In their new location they increase rapidly in size and gradually acquire the internal structures of the adult worms ; this process occupies from eleven to twenty days, the shorter period being associated with higher atmospheric temperatures. When fully grown they measure 1·5 to 2 mm., or nearly a forty-fold increase in length. In India full development has been found to take place in eleven days in the hot humid monsoon months and in eighteen to twenty days in the drier and colder winter months. The infection of *Culex pipiens* with *W. bancrofti* was found by S. M. K. Hu to last up to seventy-nine days.

If the infection of the mosquito is very heavy, the insect dies, but when it is lighter the developed young filariæ migrate to the proboscis, and are commonly found in pairs in the labium, through the thin membrane of which they escape when the mosquito feeds on the skin of the patient. They penetrate the skin and find their way to the lymphatics, where they attain to sexual maturity and thus complete their life cycle.

Microfilaria Malayi has been described in 1937 by S. L. Brug and is found in the Dutch East Indies and the Malay Archipelago, in Indo-China and China, while Iyengar considers that those met with in S. India closely resemble Brug's variety. It differs from *Mf. bancrofti* in the nuclei being more closely aggregated, the anal pore easily seen and the tail showing one to three nuclei. In S. India *Mf. bancrofti* infections are urban in character and those of *Mf. malayi* rural. In Ceylon the latter form 80 per cent. and the former only 20 per cent. of the infections. The adult worms were discovered by S. S. Rao and P. A. Maplestone in Calcutta ; they closely resemble those of *W. bancrofti* except in the number and shape of the cloacal papillæ and folds.

Filaria Ozzardi. The embryos of this worm are met with in the blood of man in the West Indies and in South America down to Argentina. They are sheathless, very active small microfilariæ with sharp pointed tails free from nuclei at the tip. They are present in the blood stream by day and by night and are considered to be non-pathogenic. They develop in *Culicoides furens* and the adult form was first found post-mortem in the mesentery by Daniels in British Guiana.

Pathology. The precise manner in which the very varied clinical

manifestations of filariasis are produced is still imperfectly understood, for it is well known that the adult worms may be present in unobstructed lymphatics, and may continue to give off immense numbers of microfilariæ for long periods without giving rise to the slightest manifestations of disease. It is equally certain that when the characteristic elephantoid enlargement of the limbs and scrotum has taken place the microfilariæ as a rule have disappeared from the peripheral blood. In the cases of infestation in which there are no symptoms the only evidence of the toxicity of the nematodes consists of a moderate degree of eosinophilia such as is common in most helminthic infections. The pathological processes which are known to produce clinical manifestations are obstruction of the lymphatic channels of a progressive nature and local inflammatory conditions associated with fever ; the latter are often due to secondary bacterial infections in which staphylococci and streptococci are usually concerned. F. W. O'Connor and C. R. Hulse have demonstrated by serial sections of excised tissues that very small amounts may contain as many as twenty-one adult filariæ in addition to fragments of degenerating ones, nearly all situated in afferent lymphatics in the capsules and cortical sinuses of glands, but rarely in the medulla. Around the dead worms they found inflammation and necrosis with enormous numbers of eosinophiles. They consider that the dead worms can produce febrile reactions in the absence of the secondary bacterial infections so frequently found by other observers (*see* p. 387). Probably septic infections play the major part in producing repeated attacks of lymphangitis leading to fibrosis and elephantiasis. Some hold that the living adult worms injure the lymphatic walls through toxins excreted by them. The clinical manifestations of the infection are brought about in the following ways :—

Lymphatic obstruction of the larger vessels is caused by inflammatory changes set up by the adult worms, which under certain conditions act as irritating foreign bodies ; this inflammatory reaction may or may not be associated with secondary bacterial infections. Ten years' records at Calcutta School of Tropical Medicine showed the admissions for filarial lymphangitis to be 40 per cent. higher in the hot humid monsoon months than in the cold season. The occlusion of the lymphatics prevents the embryos from reaching the blood stream, so that microfilariæ will no longer be found unless other adult worms are present in unobstructed vessels. Cases are on record in which the disappearance of the embryos from the blood was noted immediately after such localised lymphatic inflammation had occurred. If obstruction takes place as high up as the thoracic duct very large varicose dilatations of the thoracic and retroperitoneal lymphatics may be produced as in the classical case of Mackenzie, but such a condition can only be detected at an autopsy. Similar obstruction of large abdominal lymphatics may result in chyluria, which is due to leakage

of chyle through the distended lymphatics into the pelvis of the kidney, ureter or bladder. There may also be varicose dilatations of the lymphatic vessels of the iliac, inguinal, testicular, spermatic and external genital areas, or of those of the skin of the scrotum, labia or external abdominal wall. In this way the various forms of varicose lymphangiomatous swellings are produced ; the more superficial of these may rupture externally and cause debilitating lymphorrhœa, or even the escape of chyle (Fig. 72).

The lymphatic glands may also be the seat of considerable obstruction of the lymph flow due to a chronic fibrotic condition caused by irritation resulting from the presence of the adult worms or embryos or by inflammatory changes. It is not uncommon to find either living or dead adult worms in the glands ; the dead worms may be calcified. In Fiji Manson-Bahr found enlargement of the epitrochlear gland in 22 per cent. of the elephantiasis cases in relation to the much larger percentage of cases with involvement of the arm in the Pacific area.

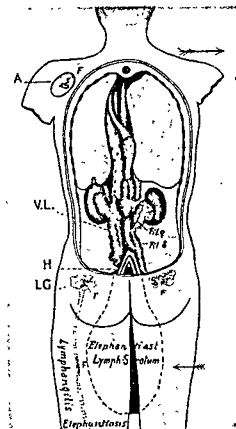


FIG. 72. Diagram of the distribution of the lesions of filariasis.

The spleen has been shown by Bombay workers in post-mortem examinations to contain small granulomata visible to the naked eye in which embryo filariæ can be found microscopically together with surrounding eosinophilia.

Elephantiasis, so common in the later stages of filarial infections, is not so easy to explain, as simple obstruction of the main lymphatic channels only produces œdema of the tissues, and not the hard fibrotic hypertrophied condition of the subcutaneous tissues combined with gelatinous œdema which is characteristic of this disease. Light is thrown on this condition by the experiments of Drinker, Field and Homans, who produced an elephantoid condition in animals by repeated injections into lymphatics of irritating substances, such as 2 per cent. solution of quinine hydrochloride, which produce obliteration of the lymph channels. Acute generalised superficial inflammation of the leg resulted, with the accumulation of highly albuminous lymph, from which a hæmolytic streptococcus could be isolated for a time. Although the proportion of persons suffering from elephantiasis in endemic areas of filariasis is

variable, the distribution of the disease is restricted to places where filarial infestation occurs, and there is a uniform association between the prevalence of elephantiasis and that of the other clinical manifestations which are known to be caused by filariæ.

The frequent absence of microfilariæ from the blood of elephantiasis patients is due to the blocking of the lymphatic vessels in which the adult worms are lodged ; this obstruction prevents the embryos from reaching the general circulation. Altogether, it is reasonably certain that these worms play an essential part in the ætiology of tropical and sub-tropical elephantiasis. Some factor in addition to lymph stasis is required to explain the production of this common condition ; the clue is found in the repeated attacks of filarial fever, which almost invariably accompany the development of elephantiasis. These attacks of fever are sudden and severe, with temperatures running up to 103° F. or 104° F. and leucocytosis ; they are frequently accompanied by localised acute inflammation of the skin, simulating erysipelas, or of the connective tissues of the deeper layers of the dermis. Many years ago the writer in Calcutta cultivated streptococci from several such cases, and also prevented for a time the recurrence of the febrile attacks by autogenous vaccine treatment. F. G. Rose in British Guiana, and others, have independently come to the same conclusions. It is also well known that the form of elephantiasis which is called *elephantiasis nostras* occurs in persons who have never lived in countries in which the filaria exists ; in the case of this disease the attacks of dermatitis and cellulitis which cause the thickening are entirely due to bacteria. A. W. Grace found filarial lymphangitis in the West Indies to be always due to a special strain of hæmolytic streptococcus. In Calcutta and elsewhere several observers have reported that dangerous cases of acute funiculitis in filarial infected patients are due to a complicating hæmolytic streptococcus. It would therefore appear that bacterial infection plays an essential part in the causation of elephantiasis, and it might be argued that there is no justification for regarding elephantiasis as a filarial disease. On the other hand, it is quite clear that there is a close association between the prevalence of filariasis and that of elephantiasis, and it is likely that the filarial worm, under certain conditions, damages the tissue in which it lives in such a way as to make them less resistant to the attack of stray circulating cocci. In other words if the filarial worm had not been present, there would have been no inflammation, and therefore no elephantiasis. From a practical point of view the filaria may be regarded as the cause of elephantiasis, although it often may be only a predisposing factor.

The great tendency to periodical attacks of filarial fever at intervals of several weeks or at monthly intervals is less easy to explain. In former days it was attributed in India to lunar influence. In 1919, the writer recorded the results of counts of the filarial embryos in measured quantities of blood taken at the same time each evening at

frequent intervals over a period of six months in the case of a number of highly infected, but apparently healthy, men in an Indian jail. It was found that a great increase in the numbers of the circulating embryos occurred *at intervals of about a month, accompanied* by the appearance of a large number of small, thin, apparently young microfilariæ, indicating that the adult female worms were giving birth to many embryos at these times. If there is no lymphatic obstruction the microfilariæ escape into the blood stream without producing any symptoms, but if the lymphatic vessel in which the adult female worm is lying is blocked, this sudden flood of young embryos will tend to block the small lymph tributaries, and, by increasing the lymph stasis, lower the resistance of the tissues and so predispose to a recurrence of the inflammatory attacks due to septic organisms. In some forms of *non-filarial dermatitis which are due to streptococci there is also* a pronounced tendency to recurring attacks ; evidently the organisms still persist after the attack is over, and are ready to spring into activity when immunity has worn off or local resistance is diminished. H. W. Acton and S. S. Rao, in Calcutta, among twenty-eight cases of filarial lymphangitis, found internal foci of infection of the gums, teeth, tonsils or intestinal ulceration in nineteen patients, and external foci in the skin in the remaining nine.

Clinical Description

It must once more be emphasised that the majority of patients who harbour the worms and have microfilariæ in their blood, even in immense numbers, are perfectly healthy, and that in places where the clinical manifestations of filariasis are frequent a considerable proportion of the apparently healthy people will be found to have the embryos in their circulation. When, however, the presence of the adult worms, combined with some other factor, has caused the obstruction of the large lymphatic vessels with varicose dilatation of the distal portions of the lymph channels, the following diseased conditions may result :

Early Symptoms. During the second world war early infections among the American forces serving in the Pacific afforded favourable conditions for studying the early symptoms of filarial infections. The principal early symptoms were lymphangitis, *lymphœdema* and enlargement of lymphatic glands after exercise, which subsided after a few days' rest. After one year's residence in highly infected endemic areas aches and pains in the testes, lymphadenopathy and funiculitis were observed. Immediate evacuation from the infected areas may result either in temporary or complete recovery due to the avoidance of reinfections, which occur repeatedly over years in the resident population in the Pacific and *other endemic areas*. Early *removal* from the area prevented the occurrence of impotence and elephantiasis even

when one-fourth of those temporarily exposed to infection in the Samoan area had shown symptoms of filarial infections. The diagnosis of early cases is especially difficult for in only 2 per cent. of suspected cases were microfilariæ found in the peripheral blood. On the other hand, no less than 85 per cent. of positive skin reactions were obtained in them, as compared with 15 per cent. of false reactions in controls.

Chyluria is the most striking result of obstruction and dilatation of the large abdominal lymph vessels communicating with the lymphatic channels which carry the chyle from the intestines. Tributaries of these rupture through the mucous lining of the urinary system, and thus the chyle escapes into the urine, and renders it milky in appearance during digestion and absorption. C. Romiti reports having watched through the cystoscope chyle escaping from either the ureter or the dilated lymphatics of the bladder mucosa. There is often some escape of blood also into the urine, which becomes rosy in tint ; the condition of hæmatochyluria is brought about in this way. The leakage may take place into the pelvis of the kidney, the ureter or the bladder, and the chylous fluid may undergo spontaneous coagulation and so cause obstruction of the ureter and retention of urine. Clotting usually takes place in the urine after it has been passed ; fine granules of fat, together with lymphocytes and red blood corpuscles, are usually present, especially in the urine secreted at night. The passage of chylous urine occurs at irregular intervals and lasts only for a few days at a time if the patient rests. In slight cases the health of the patient is not much affected, but in more serious ones the loss of such a highly albuminous and nutritious fluid gives rise to debility and anæmia. Very rarely the chyle may leak into the peritoneal cavity to produce a chylous ascites, or into the lumen of the intestine to produce chylous diarrhœa.

Lymph scrotum is another condition due to varicose dilatation of the lymphatics, resulting in the formation of numerous vesicles up to the size of a pea, or even a grape, on the surface of the scrotal skin. These vesicles may rupture and discharge clear or milky coagulable lymph for hours or days ; the total amount may be considerable ; the fluid contains microfilariæ. The loss may recur frequently over long periods ; it may necessitate the surgical removal of the diseased tissue, although this operation is liable to be followed by elephantiasis of the legs. More rarely a similar condition may affect the skin of the lower abdominal wall.

Varicose lymphatics in the groin are also common in this protean disease ; they may occur as soft swellings on one or both sides in the region of the inguinal and femoral glands and are often referred to as varicose groin glands. The tumours are often small enough to simulate hernias in this position, but they may form large masses extending down over the thighs. They differ from hernial tumours in slowly decreasing in size in the recumbent position, and slowly filling again,

in spite of pressure being maintained over the inguinal canal, when the patient stands up again, and in the absence of resonance on percussion. If punctured, a milky or blood-stained lymph will escape which may contain microfilariæ ; a similar condition has been met with in the axilla.

Varicose dilatation of the lymphatics of the spermatic cord or testicle is not very rare and fugitive swellings in the course of the lymphatics of the extremities are probably of a similar nature ; adult worms may be present in any of these situations, and are associated with the lesions.

Filarial Fever and Secondary Septic Infections. It has already been explained that neither the presence of living adult worms and microfilariæ, nor obstruction and dilatation of the lymphatic system mechanically produced by their presence, will account for the frequent sudden attacks of severe fever, often accompanied by rigor at the onset and profuse perspiration with the decline of the temperature. The presence of streptococci in the thickened superficial tissues, and the occurrence of erysipelas-like inflammation during such febrile attacks, fully accounts for the fever. It is also known that similar acute inflammation of the deep-seated varicose lymphatics within the abdomen are sometimes the cause of fatal terminal fever in filariasis ; in other cases, deep-seated lymphangitis occurs in the limbs and may result in the formation of localised abscesses due to staphylococci or streptococci. The abscesses often contain the remains of dead adult filarial worms. Such inflammatory processes may be followed by the disappearance of the microfilariæ from the blood, indicating either inflammatory obstruction of some large lymph vessel containing the adult worms, or the death of the worm. Repeated attacks of this kind are liable to be followed by steady increase in the solid œdema of the extremities, external male and female genitals, or, more rarely, the mammæ. This condition constitutes the most frequent and important clinical result of filariasis, namely, the well-known elephantiasis. Acute septic inflammation may also occur in cases of the various varicose dilations of the lymphatics of the spermatic cord and so give rise to acute funiculitis. Such attacks may prove fatal unless relief is afforded by prompt operative measures. Penicillin or other antibiotics might be worth trying. The lymphatics of the testicle or of the tunica vaginalis may be affected, giving rise to the frequent chylous hydroceles of filarial disease. Even the lymphatics of the large joints may be attacked, and, in the endemic areas of this disease, any acute inflammation of the parts liable to be infected should be suspected of being due to filariasis and investigated from this point of view.

Elephantiasis. In India and China this affects the leg most frequently, and next the scrotum, but in Fiji, Manson-Bahr found the upper extremity to be much more frequently attacked than in Asia. The penis or the labia majora may also be affected ; pendulous tumours

of a similar nature occur rather rarely in the regions of the groin, the buttock, or the scalp.

One or both legs below the knees are especially liable to be attacked and may reach an enormous size and render locomotion very difficult. The swelling first appears on the dorsum of the foot, but the ankle and leg are soon involved ; deep folds often appear at the ankle. The surface may be smooth, but frequently it becomes rough. The œdema is hard and does not pit on pressure, and if the usual filarial fever with erysipelas-like inflammation occurs, each attack is followed by increased thickening of the tissue. Similar enlargements may affect the hands and forearms, deep transverse folds are formed at the wrists, and the disease runs a similar course.

Scrotal elephantiasis is also very common, and may reach an enormous size ; the tumours, on removal, have been known to weigh over 100 lb. When a scrotal tumour has reached even a moderate size the penis becomes completely embedded in it, and the urine dribbles out of an orifice on the anterior surface. Large hydroceles often form part of the bulk of the tumour. These tumours usually have rough surfaces, and they are liable to inflammatory skin complications in the same way as those of the extremities.

The **penis** may sometimes be much enlarged with only comparatively slight affection of the scrotum—in this case it remains very prominent with a rough surface and distorted appearance.

The **labia majora** may be affected in much the same way as the scrotum, either one or both being attacked ; the breasts are sometimes involved and large pendulous tumours may result.

Diagnosis. A practitioner resident in an endemic area of filariasis will soon become familiar with the more common manifestations of the disease, such as elephantiasis, chyluria, varicose lymphatics and varicose groin glands. The occurrence of abscesses in the course of large lymphatics of the extremities will also raise a suspicion of filarial origin, and an eosinophile leucocyte increase in the blood will often help to confirm the diagnosis and allow of a favourable prognosis in the case of repeated abscesses, which might otherwise be thought to be pyæmic in nature. This blood change may be of great assistance in enabling a diagnosis of filarial fever to be made. In the case of lymphangitis and erysipelas-like inflammations of secondary septic origin, there will be leucocytosis, so that the local manifestations and the blood condition will negative a diagnosis of malaria. Calcutta workers found microfilariæ in ten consecutive cases examined at night by means of sternal puncture, but only in three of forty-six day examinations. They were fewer than in blood taken at the same time. Repeated gland biopsies in early cases among American soldiers enabled the diagnosis to be established in 60 per cent. of cases.

Fairley's Complement Fixation and Intradermal Tests. N. H. Fairley has demonstrated that an alcoholic extract of *Dirofilaria immitis* of

dogs forms an antigen which gives complement fixation reactions with the sera of persons infected with various forms of filaria. The intradermal test is a group reaction so it does not serve to distinguish between different filarial infections. In *Wu. bancrofti* infections in Porto Rico the reaction was positive in 87 per cent., but other nematodes, such as ascaris, ancylostome and trichuris must be excluded by stool examinations. In tests in 89 Calcutta patients R. B. Lloyd and S. N. Chandra obtained negative reactions in elephantiasis cases in which lymphatic obstruction cut off the toxins from the general circulation, as well as in cases of lymphangitis with both eosinophilia and polynuclear leucocytosis indicating septic complications. Positive reactions were found in cases of lymphangitis in which there was no evidence of their being due to septic complication, so the test appears to be of value in differentiating those two classes of cases. The reacting cases are not likely to benefit from vaccines.

The intradermal test is used in the same way as those for the detection of schistosomiasis and hydatid disease, but with the injection of only 0·25 c.c. of a 0·1 per cent. saline extract of dirofilaria powder, for larger doses may produce dangerous anaphylactic shock. In positive cases the immediate reaction is a diffuse erythema and a rapidly increasing wheal with peripheral pseudopodia-like extensions up to 2·3 cm. in diameter within thirty minutes, and a later œdematous swelling which may involve a considerable portion of the arm by the next day.

By X-ray examination of the limbs calcified filariæ in the form of oval areas 2 to 3 by 1 mm. in size may be seen either singly or in chains of two or more. It should, however, be borne in mind that W. P. MacArthur has demonstrated somewhat similar bodies due to the presence of calcified scolices of cystercerci in cases of epilepsy due to the presence of these parasites in the brains of British soldiers returned from India.

Prognosis. Apart from the disabilities produced by elephantoid and varicose gland tumours, the prognosis is good except when secondary septic infections, especially those of streptococcal origin, involve the extensive varicose abdominal lymphatics, and may cause death within a few days. Much may be done by surgical measures to remove the elephantoid swellings of the external genital organs, but comparatively little can be done for those of the extremities.

Treatment

In 1920 the writer showed that repeated large and somewhat toxic intravenous doses of sodium antimony tartrate rapidly reduced the number of microfilariæ in the peripheral blood, but the effect was only temporary in half the cases. P. N. Das in Puri reported the disappearance of febrile attacks, and considerable reduction in the girth of the

limbs in fifty cases of elephantiasis treated in this way but work elsewhere showed that no appreciable permanent benefit resulted from the treatment. The British Guiana Filarial Committee, under R. T. Leiper, tested a large number of drugs, and obtained the best results from antimony in reducing the microfilariæ, although they did not consider it of much value. When pentavalent antimony compounds became available a short trial of them in filariasis in Calcutta gave negative results. Later prolonged trials by Culbertson and his colleagues in Porto Rico, however, led to an important advance facilitated by preliminary tests of the drugs on a filaria inhabiting the pleural cavities of cotton rats, which was found to be killed rapidly by antimony salts, but many months may elapse before the microfilariæ disappear completely from the peripheral blood. Trivalent antimony salts had a marked effect in reducing the number of microfilariæ in the peripheral blood, but the most effective and least toxic was neostibosan given in a total dosage of 10–15 gm. over a period of up to fifty days ; this cleared the peripheral blood in from five to twenty-four months. Neostibosan is therefore the drug of choice among the antimony compounds. Possibly an intensive course of sodium antimonyl tartrate, such as has been used in schistosomiasis (*see* p. 414) might be worthy of trial in filariasis.

Hetrazan (diethylcarbamazine) has a remarkable effect on *Microfilaria bancrofti* in the blood stream by reducing the number of embryos by 90 per cent. within two minutes, but a few remain resistant to large doses and the drug has no effect on those in hydrocele fluid. An oral dose of 0·4–0·8 mg. per kilo body-weight is thus effective, although the minimal lethal dose is 10–16 mg. per kilo. It has very little action *in vitro* so Hawking suggested an opsonin-like action, which enables the leucocytes to attack the microfilariæ in the blood stream. It is too early to evaluate the drug precisely in *Wu. bancrofti* infections but mass treatment to destroy the embryo form in the blood and thus to prevent new infections is being tried as a promising use of the drug. Hetrazan (Lederle) is the same as Banocide (B. and W.) : the latter is given in doses of 150 mg. thrice daily after meals for two to four weeks. This dose is 2 mg. per kilo body-weight. For mass treatment it is given for three to five days.

Vaccines made from autogenous streptococci or staphylococci in doses of 100 to 200 millions, given at fortnightly intervals, were used by F. G. Rose in British Guiana in sixty cases, with the result that none of the milder cases relapsed, and only ten of nineteen of those which had lasted more than a year ; other workers have obtained similar results, so this treatment is of value in checking the recurring attacks of lymphangitis. In this way it is possible to retard materially the progress of the crippling enlargement of the lower extremities which is caused by elephantiasis.

Abscesses and lymphangitis are treated on ordinary surgical lines.

Several observers have reported the rapid subsidence of acute febrile filarial lymphangitis under treatment with sulphonamides ; doubtless due to its action on the secondary streptococcal infection. In filarial abscesses, due to staphylococci, these drugs failed. Penicillin is of great value in these conditions. Chloromycetin and aureomycin are also worthy of trial.

It is very generally agreed that varicose groin glands should not be interfered with surgically, as their removal is likely to be followed by elephantiasis of the lower extremities and exhausting lymphorrhœa.

Elephantoid tumours of the scrotum or labia majora may be removed when they reach a size which greatly inconveniences the patient, but warning should be given that a similar condition is liable to arise in the legs after such a procedure.

Elephantiasis of the legs is less amenable to treatment if advanced. In the early stages, as long as the swelling is essentially due to limited œdematous swelling of the subcutaneous tissues, considerable amelioration of the condition may be obtained by rest and elevation of the affected limb as much as possible, combined with regulated pressure by means of elastic stockings or careful bandaging. The striking effect of pressure is obvious in the case of persons who have continued to wear boots while the disease is developing in the legs ; the feet may remain normal in size while the legs are becoming greatly enlarged.

Operative measures may be required in more advanced cases with fibrosis as well as œdema of the subcutaneous tissues. They are based on the principles of removing as much as possible of the thickened tissues together with promotion of a better flow of lymph by affording communication between the superficial lymphatics and the deep ones in the muscles. Kondeleon's operation consists in removing long strips of the hypertrophied subcutaneous tissues ; Auchincloss in addition removes a strip of the deep fascia for the length of the lower leg. W. Junge has reported improved results by a more extensive operation on similar lines. He makes an incision along the anterior edge of the tibia from the knee to the ankle with cross ones above and below. The skin is then reflected on each side for one-third of the circumference of the leg leaving one-third at the back untouched. Rings of the thickened tissues are dissected off the deep fascia from above downwards and about twenty-five windows a little larger than a postage stamp are cut in the exposed muscular fascia to allow of the establishment of anastomosis between the superficial and deep lymphatics of the limb. Hitherto the common occurrence of streptococci in the œdematous tissues has frequently led to septic complications after such operations, but there is already evidence that these can often be prevented by the administration of sulphonamide drugs for a few days before and after operation. The same principles will apply to the much rarer elephantiasis of the upper extremity.

Prophylaxis. As it is usually those who show no signs of disease

who harbour most microfilariæ in their blood, the only feasible method of prevention for those who must reside in the endemic areas is to rely on the use of mosquito curtains at night throughout the year. In the case of Europeans the farther they live away from the indigenous population the less likely they are to be infected; they should not overlook their own servants, any of whom may be a source of infection. In Fiji R. W. Paine has reported the successful introduction as a prophylactic measure of the harmless mosquito, *Megarhinus*, which breeds in tree holes, etc., where its predacious larvæ destroy those of the only mosquito carrier of filariasis in that region, *Aëdes scutellaris*. In an area of Southern India, with only *Mf. malayi* infections, the disease was effectively controlled by clearing the water plant, *Pistia stratiotes*, from the root air cells of which the larvæ of the insect carrier, *Mansonioides annulifera*, obtain oxygen.

OTHER FORMS OF FILARIASIS

LOAIASIS

Definition. A human infection with the filaria *Loa loa*, which is widespread from West Africa across to the Anglo-Egyptian Sudan and in the Congo basin. It produces small tumours known as Calabar swellings in many parts of the body and is frequently found in the ocular region.

Ætiology and Mode of Infection. The adult worms are shorter and thicker than *Wu. bancrofti* and have a tuberculated cuticle. The microfilaria is sheathed and differs little from that of *Wu. bancrofti* except that the tail shows an acute bend and the nuclei reach its tip. It is found in the blood during the day in much larger numbers than at night, a feature which led Manson correctly to suggest the day-biting fly, *Chrysops*, as its probable carrier, Leiper verified this surmise in 1913 by demonstrating the development of the microfilariæ in the thoracic muscles of *C. dimidiata* within ten to twelve days and infection takes place as with *Wu. bancrofti*. It appears to take three or four years for the adult worms to reach sexual maturity and the adults live for many years in infected persons. The first symptoms of the disease may thus appear long after the patient has left the endemic area. The filariæ may die and become calcified and thus be evident on X-ray examination. The worms do not block the lymphatics, but wander in the connective tissues especially in the neighbourhood of the eyes and may sometimes be visible under the skin or conjunctiva.

Symptoms. The movements of the worms may produce intense irritation and may require removal if in or near the eyes.

Calabar swellings present the most characteristic feature of the disease; they are temporary painless œdematous tumours up to the size of a hen's egg and contain adult worms. They do not suppurate or cause much trouble, but may be numerous and recur over a period

of years in the subcutaneous tissues of many parts of the body especially in the arms. They arise suddenly and disappear gradually after a week or more. Aspiration of the swellings may yield serum containing many embryos produced by the wandering female worms. It has been suggested that the symptoms may be due to local anaphylactic reactions.

Diagnosis may be made by finding the worms under the skin, by the appearance of Calabar swellings or by finding microfilariæ in the bloodstream. The eosinophiles are increased in numbers and may amount to 50–70 per cent. The complement-fixation and intradermal tests described on p. 391 are positive in a large proportion of cases.

Treatment. Adult worms in the neighbourhood of the eye should be removed after first fixing them with a forceps or by a thread passed under them with a needle. Calabar swellings are evanescent and rarely require active treatment other than cooling lotions or adrenalin injections to allay irritation.

Hetrazan may be given orally in doses of 1 mg. per kgm. body weight three times a day for ten to twenty days up to total amounts of 1·0–10 gm. with only temporary reactions in the form of itching and rashes which are alleviated by 50 mg. doses of benadryl. After this treatment cases have remained free from symptoms up to over six months if they did not re-enter the endemic area.

ONCHOCERCIASIS

Definition. A disease due to the nematode worm, *Onchocerca volvulus*, which produces multiple small tumours containing the adult worms in the subcutaneous tissues and whose embryos are found in the skin and in the eye often with resulting blindness.

Ætiology and Mode of Infection. The adult worms are filiform tapering at both ends and males are more numerous than females in the cystic tumours. The tails of the females are embedded in the tissues and so are difficult to remove whole. The worms show annular thickening of the cuticle. Males measure 20–30 mm. in length and the females 335–400 mm.

The microfilariæ have no sheaths and are rarely found in the blood stream. They are found in the skin, especially in the neighbourhood of the small tumours containing adult worms. They are numerous in all parts of the eyes. They are ingested by small black biting flies, especially the *Simulium damnosum* and develop in the thoracic muscles of the insects. Infection of man takes place through bites of infected flies in the day time. African antelopes, cattle and buffaloes may be infected and present small tumours as in man.

Incidence. This parasite is widely distributed in West Africa, the Congo area and in East-African provinces of Uganda, Kenya and Nyasaland. It is also common in Mexico and Central America,

especially in Guatemala where the tumours are more frequent in the head than on the rest of the body.

Symptoms. The subcutaneous cystic tumours measure from one-fifth to one inch in diameter and are usually about the size of a pigeon's egg. In Nigeria Dyce Sharp found the tumours in 30 per cent. and embryos in the skin of 55 per cent. of the people, but the cysts are not numerous and cause little pain or inconvenience. In the African form they are most commonly met with in the axilla, about the elbow and in the popliteal space where the lymphatics converge. They are not adherent to the connective tissues so can easily be removed. Enlargement of the scrotum has also been attributed to this parasite.

Eye infections are of greater practical importance on account of the frequency of resulting blindness due to punctate keratitis, choroiditis, iritis, cyclitis and optic atrophy produced by the presence of microfilariæ in large numbers in the lymphatics. The embryos may be found by puncturing the anterior chamber of the eye under cocaine or they may be demonstrated by means of a slit-lamp microscope or the ophthalmoscope.

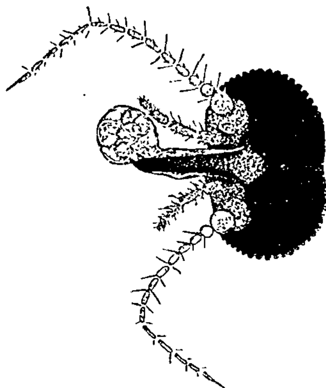


Fig. 73. Fully developed larvæ of *Filaria perstans* in the proboscis of *Culicoides austeni* (Dyce Sharp).

Diagnosis may be made by finding the microfilariæ in the eye or skin or in flies fed on infected skin. The eosinophiles of the blood are increased.

Prognosis is good except as regards eye infections or in cases with large numbers of tumours, septic infections of which may occur. Prevention is difficult owing to the simulium being able to pass through mosquito curtains.

Treatment. The small tumours can easily be removed under a local anæsthetic, especially those in the neighbourhood of the eyes. Such antimony preparations as tartar emetic or Fouadin have been recommended and recently hetrazan has been tried, but Hawking and Laurie found this drug to be very toxic in full doses. The reactions

appear to be in proportion to the number of embryos in the skin, so the drug is of doubtful applicability for mass treatment. After a reaction it is better tolerated. Further cautious trials are indicated.

Acanthocheilonema perstans or *Filaria perstans*, is widely distributed in West Africa, the Congo and Uganda. It is also met with in South America from Venezuela southward to Argentina. The adult worms inhabit serous cavities and the mesentery and retro-peritoneal connective tissues. The microfilariæ are found in the blood by day and by night; they develop in midges, *Culicoides austeni*, as was shown by Dyce Sharp, in the same way as *Wu. bancrofti* do in mosquitoes; they escape from the proboscis of the insects during feeding and enter the skin, so causing infection (Fig. 73).

This form of filariasis is generally considered to be harmless, but Molson thinks it may produce fever and he advises intravenous injections of 2–10 c.c. of a 1 per cent. solution of methylene blue to cause the microfilariæ to disappear from the blood.

GUINEA-WORM DISEASE OR DRACONTIASIS

Definition. The invasion of the connective tissues by a nematode worm, *Dracunculus medinensis*, the female of which comes to the surface, where it causes a blister, usually on the lower extremity; when the blister bursts there is an escape of the embryos. Rupture of the worm within the body is liable to be followed by serious septic cellulitis.

Distribution. This disease occurs in extensive areas of Western India and South-west Asia, Northern and Central Africa from the Nile Valley and Uganda through the Sudan across to West Africa, and also in small areas of tropical South America. In Turkestan L. Issajev found 5 per cent. of dogs infected with guinea-worms, and he produced the disease in them by feeding on infected cyclops. It is often very local in its incidence, occurring only in certain villages, where up to 80 per cent. of the people may be infected and suffer for a month or more (Fig. 74).

Ætiology. The causative parasite is *Dracunculus medinensis*, formerly known as *Filaria medinensis*. The female measures from 12 to 48 inches in length and one-seventeenth of an inch in width; it is sometimes visible just beneath the skin as a long, very thin, wavy, white band. The uterus contains an immense number of unsheathed embryos 0·5–0·75 mm. long and 0·02 mm. broad, with a tapering tail and coiled-up bodies; these escape from the lower extremities of man into water as free-swimming forms, and then enter certain kinds of cyclops, or water-fleas, to undergo further development. They regain access to the human body when drinking water containing an infected cyclops is swallowed. The hydrochloric acid in the stomach kills the cyclops, and the larvæ escape and make their way into the tissues.

They take about a year to reach the reproductive stage and so complete their life cycle.

Symptoms. Before the occurrence of local symptoms there may be a transient urticarial eruption, sometimes accompanied by vomiting. Shortly afterwards the female worm makes her way to the surface of the body, usually in the region of the feet and legs. Whatever be the cause of her selecting this part of the body, there is obviously a better prospect of survival of the species than if some other region had been chosen, as the escaping embryos have an excellent prospect of reaching the water in which the life cycle is continued. Before the worm reaches the surface there may be a certain amount of indefinite aching pain in the affected part, but often the first manifestation is the formation of a small blister on the skin at the place where the anterior end of the worm is seeking to come to the surface. Those who have once suffered from the disease can usually tell when a worm is nearing the surface, as they have a burning or itching sensation at the spot. There is usually some degree of eosinophilia. When the blister bursts the embryos either escape through the opening or the thin transparent uterus is itself protruded; this ruptures and allows the escape of a milky fluid containing numerous embryos. A little fluid escapes from time to time when the affected part is in contact with water until the uterus is completely emptied. When all the embryos have escaped, a process which takes several days, the remains of the worm become absorbed without harm to the host. If the worm fails to come to the surface and discharge its embryos it may die in the tissues and become calcified, when it can be detected by X-rays. The calcified worms are said by F. P. Connor to produce at times rheumatic pains, synovitis or periostitis, and in some cases it is desirable to remove them. Acute purulent arthritis of the knee joint of an aseptic nature, and consequently amenable to treatment by aspiration, has also been described. As long as no bacterial infections ensue the symptoms produced by this parasite are mild and do not endanger life or seriously menace the health of the host.

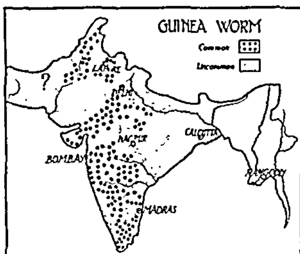


Fig. 74. Map of distribution of guinea-worm in India.

Secondary Septic Infections. As in the case of *Wu. bancrofti*, the greatest danger in these cases is septic infections with acute cellulitis

at the sites of the parasites. Occasionally this may take the form of abscess formation without the worm having perforated the skin, and this is likely to occur if the uterus of the worm is ruptured subcutaneously, as the irritating secretions produce inflammation. More frequently this serious complication results from the rupture of the uterus after perforation of the skin has taken place, often as the result of injudicious and rough attempts to extract the worm before the uterus has emptied itself, and while the terminal hook is fixed deep down in the tissues. Staphylococci or streptococci now find their way from the surface into the inflamed tissues, and a dangerous, sometimes fatal, acute cellulitis results.

Diagnosis. The intradermal test (*see* p. 391) was found by G. W. St. C. Ramsay in Nigeria to give positive results in 85 per cent. of guinea-worm cases, and 84 per cent. of negative reactions were obtained in control cases, but the results are still positive long after recovery.

Treatment

Tartar emetic, intravenously, was reported by Macfie to kill the adult worms, but this has not been confirmed. Injections of perchloride of mercury into the worms when visible under the skin have not met with much success ; it is better to avoid active interference until the adult female commences to discharge the embryos through the opening in the small superficial ulcer which results from rupture of the blister on the skin. Repeated pouring of cold water over the site of the worm will hasten the discharge of the embryos, and if the worm protrudes from the opening, as is commonly the case, a small piece of silk thread may be tied to the worm and to a small piece of wood, on which the worm is wound day by day with gentle traction. If too much force is used the result will be disastrous rupture of the worm with accompanying acute cellulitis. Owing to the risk of this accident some think it best to abandon this old Indian method of extracting the worm. Once the embryos are all discharged no further trouble is likely to occur, and only a simple antiseptic dressing is required for the ulcer.

Suitable surgical treatment is needed if cellulitis occurs.

Prophylaxis. As infection only occurs by drinking water which contains the infected cyclops, prevention is simple in theory, although difficult in practice among ignorant village people.

Wells and tanks which are approached by steps are the greatest source of infection. No one should be allowed to drink water from these, but from draw-wells which are surrounded by a proper parapet to prevent water which has become infected from running back. It is still better to introduce pumps for drawing water instead of buckets.

R. T. Leiper found that heating well-water to 65° C. by steam killed the cyclops, but as this would have to be done weekly the expense is prohibitive, in India at least. The addition of caustic

potash, quicklime, or of potassium permanganate has been recommended for this purpose. *As the carrier water-fleas are visible to the* naked eye, straining drinking water through coarse calico, such as the villagers use for clothing, is the simplest and most practical method of avoiding infection. V. N. Moorthy has advised stocking infected wells with a fish belonging to the species *Barbus puckelli*, which preys on the cyclops. The fish must be renewed yearly in those wells that dry up in the hot season.

LEONARD ROGERS.

CHAPTER XXI

SCHISTOSOMIASIS AND OTHER HELMINTHIC DISEASES

Definition. Schistosomiasis is the name given to a group of diseases caused by the presence of certain trematode worms in the abdominal veins; the ova of these worms damage the genito-urinary and intestinal mucous membranes and the liver.

Historical. The most widely distributed urinary form of the disease is known to have been present in Egypt some 3,000 years ago, as A. Ruffer found the characteristic ova in ancient Egyptian mummies. The worm which causes the widespread endemic hæmaturia of Egypt was discovered in 1851 in Cairo by Bilharz, and was long known as the *Bilharzia hæmatobia*, but under the rules of international zoological nomenclature it is now called *Schistosoma hæmatobium*. The ovum of this species has a sharp terminal spine, which enables it to pierce the wall of the bladder and escape into the urine, which becomes blood-stained. From the time of Bilharz onwards it was observed that lateral-spined ova also occurred, and Sonsino first suggested that they belonged to a different species of worm. Patrick Manson, in 1903, found only lateral-spined ova in the fæces of a patient from the West Indies. It was not until the full life histories of the two species were worked out later by R. T. Leiper that the lateral-spined ova were generally acknowledged to come from a distinct species of worm, *Schistosoma mansoni*, whose eggs work their way almost exclusively through the mucous membrane of the lower large bowel to appear in the fæces, and thus produce the intestinal form of the disease. Both varieties are met with in Egypt and some other parts of Africa.

A third variety, *Schistosoma japonicum*, occurs in the Far East; its spineless ova were first found in 1904 by Katsurada in the fæces of a patient in Japan. These give rise to a ciliated miracidium in water, the adult worms of which were soon after found in the portal veins of dogs, cats and man in Japan, and by Catto in Singapore. They produce the Katayama disease of Japan, characterised by a fatal form of cirrhosis of the liver.

The discovery of the snail as the intermediate host of schistosomes was first made in the case of the Japanese variety. The experiments of Fujinama and Nakamura in 1907–10 showed that mice and other animals could be infected by the parasite if they were immersed in the water of some ricefields which were believed to be dangerous to man, and Matsuda proved that man himself might similarly be infected through immersing his legs in the water. A great advance was made when, in 1923, Miyairi and Suzuki succeeded in infecting snails with the miracidia. In the following year Ogata described the structure of the cercaria, and in the same year R. T. Leiper and Atkinson visited

the Far East and traced the development of sporocysts containing daughter cercariæ in the liver of the infected snails. These workers also demonstrated the penetration of the skin of mice by the cercariæ and the development of the adult worms in the mesenteric veins of mice or hamsters.

In 1925 Leiper, working in Egypt, observed the development of the miracidia of *S. hæmatobium* in the fresh-water snail *Bullinus*; in the following year he showed that those of *S. mansoni* developed in another water-snail, *Planorbis*. He demonstrated that the cercariæ thus obtained differed in some particulars from those of the *S. hæmatobium*, and, on infecting mice and monkeys with cercariæ derived from the lateral-spined ova, the adult worms also differed in their minute anatomy from the *S. hæmatobium*, which is derived only from the terminal-spined ova. He thus established finally the distinction between these two varieties of parasite worms and at the same time furnished invaluable information from the prophylactic point of view. This important work has been confirmed by others, and Manson-Bahr and Fairley found that certain waters, which are inhabited almost solely by *Bullinus* snails, infected bathers with worms producing terminal-spined ova, and not with *S. mansoni*; these findings are in accordance with the observations of Leiper. Lutz, in Brazil, and Iturba, in Venezuela, have traced the development of *S. mansoni* in varieties of planorbis which are found in those countries. In Mauritius A. R. D. Adams (1934) found *Bullinus forskali* to be the carrier.

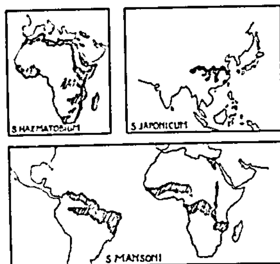


FIG. 75. Maps of distribution of Schistosomiasis.

Geographical Distribution. **S. japonicum** has a well-defined distribution in Eastern Asia, including localised areas in South Japan, an extensive area of the valley of the Yangtse River and its tributaries in Central and Southern China, portions of the Philippine Islands, in Singapore and Malaya among the Chinese, and a few cases have been reported by Cullen from the Shan States of North-east Burma, which is as far west as this species is yet known to extend (Fig. 75).

S. hæmatobium is very widely distributed in Africa along all the north coast. It extends through Egypt, Abyssinia and the Sudan right down the east coast to the Union of South Africa, where it is very prevalent. It occurs in West Africa from Senegambia to Nigeria and

to South-central Africa. The parasite has also been found in South-west Asia from Arabia and Palestine to Iraq.

S. mansoni is also widely distributed in Africa ; it co-exists with *S. hæmatobium* in some parts of Egypt, the Sudan and East and West Africa, and extends down the Congo basin to Rhodesia, Nyasaland and Portuguese East and West Africa. In addition, it is found alone in the West Indies and the whole of the north of South America, from Venezuela, through Guiana to the Amazon Valley and the north coast of Brazil (*see* Fig. 75).

S. intercalatum is another species, first suspected by C. C. Chesterman in the Belgian Congo, the ova of which were described by A. C. Fisher in 1934 as having the anterior spine of *S. hæmatobium*, but being intermediate in length between those of that species and the much longer ones of *S. bovis* of sheep. It is common in Gabon. It produces a mild form of intestinal infection in children and yields to tartar emetic, anthiomaline, fouadin and acriflavine treatments.

Epidemiology. As the infection of the three forms of human schistosomiasis is contracted through bathing or wading in water containing infected snails, the epidemiology of all can conveniently be considered together. Both urinary and intestinal schistosomiasis in Egypt and elsewhere occur where stagnant or slow-flowing water, such as that of canals and irrigation channels, harbour the species of fresh-water snails in which the respective worms can develop. In areas where perennial irrigation has been introduced 60 per cent. of the population are infected, but where the old basin irrigation from the flooded Nile still obtains only 5 per cent. suffer. The disease was nearly absent from the Gezira area of the Sudan until after the opening of the Sennar irrigation dam on the Blue Nile, within a year or two of which all the irrigation canals became infested with schistosome-carrying molluscs. The water is infected by pollution with the excrement of persons who pass the ova, from the eggs the miracidia hatch out, and so the snails become infected, and in their turn discharge enormous numbers of cercariæ, which penetrate the skin of human beings who come into contact with the contaminated water. Rapidly-flowing streams seldom harbour the snails which serve as the intermediate hosts. Brackish water is usually free from them, except in the case of *P. glabratus*, a carrier of *S. mansoni*. A fairly warm climate is necessary for the life cycle of the parasites, and so a limit is set to the geographical distribution of the diseases produced by them. Children are most liable to be infected, because of their habit of bathing and paddling, and adolescent and adult agricultural labourers are also exposed by being brought into frequent contact with stagnant water, especially in ricefields. Those who shoot in the same localities sometimes become infected.

In the case of *S. japonicum* of the Far East infection is commonly due to bathing in canal waters or wading in ricefields, the water of which is contaminated by the excreta of man or certain domestic animals,

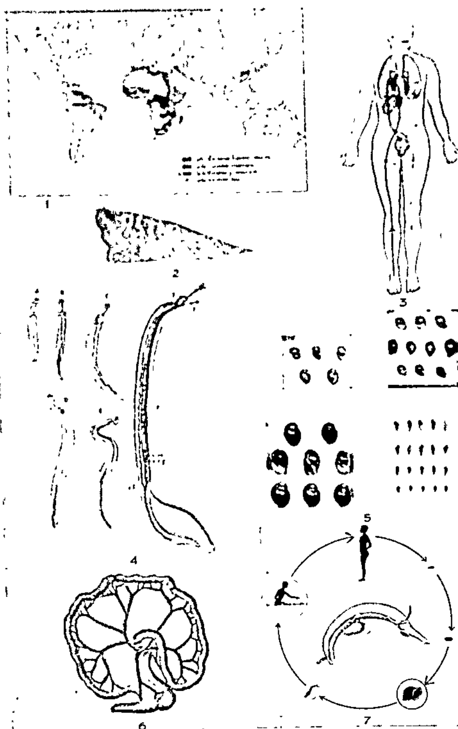


FIG. 76. (1) Map of the world distribution of Schistosomiasis. (2) Liver of mouse experimentally infected. (3) Diagram of the route of infection through the body. (4) Male and female adult and developmental forms of Schistosoma hæmatobium. (5) Some of the snails in which Schistosomes develop. (6) Mesentery of mouse experimentally infected with bilharzia. (7) Diagram illustrating infection of snail with miracidia hatched-out from ova and of man by cercariæ escaping from the snail into water.

such as cattle and buffaloes, 12–18 per cent. of which may be infected. Horses, pigs, goats, dogs, cats and field mice may be other sources of widespread infection of water, which, together with the Chinese custom of using human excreta for fertilising soil, makes the control of this helminthic infection extremely difficult.

Ætiology. To supplement the facts stated in the historical section a brief description will be given of the life history of the common *S. hæmatobium*, and of the more easily recognised external features in which the other two forms differ from it. The male *S. hæmatobium* measures 1·5 cm. in length by 1 mm. in breadth. *S. mansoni* is only 1 cm. in length, and *S. japonicum* is still smaller, measuring 0·9 cm. by 0·6 mm. All three male worms are characterised by being flat, with thinner leaf-like extensions which are folded ventrally to form the gynæcophoric canal, in which the longer rounded female worm is clasped with the aid of numerous fine tubercles present on the cuticle of both the dorsal and the ventral aspects of the male. These tubercles are larger in the case of *S. mansoni*, but are absent from *S. japonicum*.

The female worms are rounded and are much longer than the males; they measure from 2 cm. in the case of *S. hæmatobium*, to 1·2 cm. in *S. japonicum*, so their ends project beyond the gynæcophoric canals of the males. The uterus of *S. hæmatobium* contains many terminal-spined ova, measuring 160 μ by 50 μ, but that of *S. mansoni* only shows one to three laterally-spined eggs, 150 μ by 70 μ, and that of *S. japonicum* contains up to 300 smaller non-spined ova measuring 70 μ by 40 μ. Both male and female worms have two ventral suckers anteriorly, by which they adhere to the inner surface of the abdominal veins.

When the urine or fæces containing these ova are diluted with several times their bulk of water the reduced osmotic pressure causes the shells of the ova to rupture and so set free the oblong finely-ciliated free-swimming embryos. These seek out the appropriate snails and penetrate the skin of the head region, and especially of the antennæ. They now lose their cilia and develop into sporocysts; by the end of six days they have grown much larger in size and give rise to daughter sporocysts in the form of thin-walled, long, oval, slowly-moving branching bodies. The majority of them eventually find their way into the liver, which in time becomes so full of them that its yellowish appearance may be evident to the naked eye. In from five to six weeks after infection of a snail large numbers of very active cercariæ develop in the daughter sporocysts. The cercariæ bore through the tissues of the host, and escape in large numbers from the pulmonary chamber of the snails to reach the water once more, ready to invade the tissues of a convenient human host. They can be seen with the naked eye swimming in water as white, thread-like bodies; they can live in fairly warm water with a good supply of oxygen for over twenty-four hours, and are attracted by light, also by any movement

of the surface of the water, or by the presence of man or any animal, including mice, rats, guinea-pigs and monkeys, in which they can develop. They penetrate the skin of the host, dropping their tails in the process, and next pass to the liver through the blood or lymph vessels. *In experimental animals mature adult worms are found six* weeks after infection in the abdominal veins. According to N. H. Fairley and P. Manson-Bahr, the adult worms in experimental monkeys travel to the distal ends of the veins, where the narrower female leaves the male and enters into the smallest vein possible, where her eggs are deposited. The eggs make their way, with the help of their spines, into the bladder or the lumen of the intestine, as the case may be.

Pathology. The invasion of the human host by large numbers of schistosomes first produces constitutional symptoms, but the most typical pathological reaction is the accumulation of eosinophile leucocytes at the sites where the ova are deposited in the tissues ; at the same time there is an increase in the eosinophiles in the peripheral blood stream. The local lesions are dependent on the situations which are invaded by the migrating ova ; these vary according to the species of the parasite, and so they require separate description. At autopsies or operations the gall-bladder has occasionally been found to be infected by *S. hæmatobium*, or *S. mansoni*. H. B. Day has reported a case in which the lungs after death showed many granulomata containing eggs and also coupled *S. mansoni* worms in dilated arteries. The frequency and importance of pulmonary infections with both *S. hæmatobium* and *S. mansoni* in Egypt is illustrated by 33 per cent. of infections and 2 per cent. of deaths found in 282 autopsies by Shaw and Ghareeb. Embolisms formed by the ova produce parenchymatous tubercles in the lungs and focal and diffuse damage to the pulmonary arteries. The latter may induce atheroma, followed by fatal hypertrophy and dilatation of the right heart as in Ayerza's disease.

In **urinary schistosomiasis** due to *S. hæmatobium* the vast majority of the ova are found in the genito-urinary system, and they very rarely appear in the fæces, so the pathological lesions are found in the former region, in the tissues of which the irritating eggs accumulate in enormous numbers, especially in the mucous membrane of the urinary bladder. In the early stages the mucosa, especially of the posterior wall of the bladder, shows minute papules with congested bases, which later merge to form a red patch with small pale points. Later still the mucous membrane becomes thickened and has a fine granular surface ; there are also congestion and catarrh of the mucosa. These changes are due to the presence of innumerable ova, many of which are calcified. The bladder wall may now show much fibrous thickening with contraction of the lumen of the organ, or vesical polypi may develop. Calculi often form with ova as their nuclei, and malignant tumours may result from the chronic irritation of the mucosa. In advanced cases there may be thickening of the ureters, with secondary hydronephrosis and de-

generation of the kidneys ; the urethra, prostate and seminal vesicles may also be involved in the disease. More rarely, heavy infections are said to cause cirrhotic changes in the liver, although these are much less frequent then in the other forms of schistosomiasis. Ova have also been found in the spinal cord and brain with symptoms of paraplegia, etc.

In **intestinal schistosomiasis** due to the *S. mansoni* the disease chiefly affects the lower part of the large bowel, and to a less extent the liver. The ova invade the large intestine, especially the rectum and sigmoid, instead of the bladder wall. Here the pathological changes are similar to those of the bladder, namely, thickening and infiltration of the mucosa with congestion and small hæmorrhages. There is also a formation of papillomatous tumours of the rectal mucosa ; these contain numerous ova, and dysentery occurs in severe cases. In this form the liver contains many ova, which produce minute white nodules composed of fibrous tissue containing numerous ova of *S. mansoni*, while young worms are found in the portal veins. A peculiar form of cirrhosis of the liver develops in the later stages ; in this there is not much contraction or nodulation of the surface of the organ, but pale elongated fibrous-tissue areas are formed which have been compared by Symmers to the stems of clay pipes.. The spleen may become enlarged and contain ova.

In **Asiatic schistosomiasis** due to the *S. japonicum* the main stress of the pathological process falls on the liver, for the cercariæ after entering through the skin pass to the lungs, then travel to the liver, possibly by burrowing through the mediastinal tissues, or more probably they are carried by the circulation ; they reach maturity in the portal system. The ova are deposited in the small tributaries of the mesenteric veins ; some of them pass through the mucous membrane of the large intestine to reach the lumen of the gut and escape in the fæces, but many are carried back to the liver ; these may even reach the general circulation, and cause small emboli, sometimes affecting the brain. Cirrhosis of the liver of the atrophic variety is produced, partly by mechanical irritation, but also by the toxic products of the parasites, and the spleen shows great fibrotic enlargement. The abdominal lymphatic glands are enlarged and contain ova ; the large bowel shows changes similar to those of intestinal schistosomiasis, with thickening and papillomatous changes in the mucous membrane and sometimes superficial ulceration.

Clinical Description

URINARY SCHISTOSOMIASIS

In the variety of schistosomiasis which is due to the *S. hæmatobium* the brunt of the symptoms falls on the genito-urinary system, but their degree varies very greatly, from early and mild cases in which

there are no definite clinical signs, to severe cases in which there is fatal disorganisation of the bladder, ureters and kidneys, largely due to secondary bacterial infections.

The invasion of the system by the parasites may be accompanied by toxic signs. These are best seen in primary infections of Europeans: they are rarely noticed in the infected indigenous population. They consist of pruritus and urticaria with fever and abdominal pain and some loss of weight; they appear about a month after exposure to infection and are common to all the forms of the disease. After the worms have reached maturity in the body the urinary symptoms may be absent for a variable time, and the presence of the parasites can only be detected by finding the ova in the last few drops of urine, which may also contain a little blood. According to Campbell Begg the ova are seldom found in the urine in the early stages, even in cases in which the lesions in the bladder are easily detected by cystoscopy. These latent cases may be sources of infection. The first symptom observed is usually slight hæmaturia unattended by pain; this may last for years and be attended by greater debility than the small loss of blood accounts for. Occasionally more extensive hæmorrhage may produce clotting and retention of urine. As the involvement of the bladder wall becomes more extensive, irritation increases, and there is a burning sensation at the end of micturition. Urine is passed frequently and the last portion contains blood. At this stage there is contraction of the cavity of the organ. The urine may show flocculi and white thread-like pieces of mucus or small blood clots containing numerous ova. Rarely a large hæmorrhage may be accompanied by the passage of the worms. If the rectum is involved there may be slight dysenteric symptoms; these are usually due to the existence of a double infection in which *S. mansoni* is also present.

Progress and Complications. The foregoing symptoms may persist for years, and in the absence of complications they may gradually become less evident, although their complete subsidence is unusual. In other cases more serious trouble arises through increasing inflammation of the bladder, often due to secondary bacterial infections; these not infrequently end in the death of the patient. Stone in the bladder may result from the deposit of salts around the spined ova, or sand-like deposit is formed on the roughened mucous membrane of the viscus. Septic infection may occur; this often spreads up the ureters to the kidneys, which may be in a state of hydro- or pyo-nephrosis. Papillomatous growths in the bladder are very common; these contain numerous ova. A case of transverse myelitis has been reported in which calcified schistosome ova were found after death in the swollen lower end of the spinal cord. Latent schistosome involvement of the lungs may be revealed by X-rays, and bronchial asthma may occur.

The ureters may be infiltrated and thickened by the deposit of the ova, especially in their lower portions: they are sometimes dilated;

the kidney rarely shows schistosome infection, but suffers from secondary complications of a serious nature. The prostate and seminal vesicles are sometimes infected with the ova, and the semen may be blood-stained and contain ova. The **urethra** is similarly infected and becomes thickened, sometimes to such an extent that a pseudo-elephantiasis is formed ; urinary fistula may occur in the perineum or in the penis itself, with tortuous urethra and great thickening of the organ, including the glans, which may result in urethral stricture.

In **females** various complications have been met with, including vesico-vaginal fistula, sand-like deposit, fibrosis and ulceration of the hymen and vagina, warty and papillomatous growths of the clitoris, vulva, cervix uteri, ovaries and fallopian tubes.

The lungs may contain the ova ; hæmoptysis sometimes occurs and gives rise to a suspicion of tubercle of the lungs, but the sputum will be found to contain schistosome ova. The ova have also been found in the brain and have at times caused paralysis or fits in heavily-infected patients.

The **blood** in both forms of Egyptian schistosomiasis shows a characteristic great increase of the eosinophile leucocytes averaging from 16 to 24 per cent. ; the polymorphonuclears are somewhat reduced, the total count being slightly increased to about 10,000. The anæmia is slight, except in extreme cases, average counts being 4,500,000 red corpuscles, with over 80 per cent. of hæmoglobin and a normal colour index. In advanced cases with secondary septic complications the eosinophile increase may be slight or absent and the polymorphonuclears may be high.

Diagnosis. *In places in the endemic areas, such as Egypt,* about half the population may be infected with *S. hæmatobium,* most of the patients show no symptoms in the early stages ; in these the diagnosis *can only be made by microscopical examination of the* last few drops of urine passed into a separate vessel. Cystoscopic examinations are of value in the early diagnosis and as a test of cure ; some observers insist that the absence of ova from the urine does not prove that the patient has been cured. Patients coming for treatment in moderately developed cases usually complain of passing a little blood at the end of micturition ; in this ova will be found by the usual methods of examination of the sediment or of the deposit after centrifugalisation. Any symptoms referable to the urinary tract should arouse suspicion when they occur in persons who live in an endemic area of the disease.

A careful examination of the urine for the eggs will usually complete the diagnosis, but it must be remembered that symptoms of organic disease produced by the parasites may remain after the adult worms have died. In such cases ova may be scanty or absent, *and if present* they are liable to be black and degenerated or calcified. These dead ova will fail to hatch out when the urine is diluted with water. Occasionally small numbers *of terminal-spined S. hæmatobium* may be

found in mucus on the surface of stools, or in a rectal swab, even in cases in which the dysenteric symptoms are absent. The condition of the bladder wall may be ascertained by cystoscopic examination and renal efficiency tests are of value in advanced cases to determine the functional capacity of the kidneys. A considerable increase of the eosinophile corpuscles in the blood may point strongly to the existence of the disease if other causes like ancylostomiasis can be excluded, but as both diseases are extremely common in Egypt this clue loses much of its value.

Complement Deviation Test. This is a group reaction common to all forms of schistosomiasis. The antigen is an alcoholic extract of cercarial-infected livers of snails infected with human or animal schistosomes. Some observers have reported positive reactions in a large percentage of infections, including early cases and those infected by male worms only. The test is also of value in determining cures, when negative reactions are obtained.

Fairley's Intradermal Test. Similar antigens are given as intradermal injections, which in positive cases result in the appearance of within about ten minutes of a large white wheal at least 4 mm. in diameter surrounded by erythema in 98 per cent. of infections.

Prognosis. When suitable treatment is adopted this is very good in all cases in which no serious organic or secondary septic changes have taken place. With the antimony treatment the parasites are quickly destroyed and the ova disappear or become calcified. Unfavourable conditions are, old age, severe anæmia with hæmoglobin below 30 per cent., very frequent micturition, and especially septic complications. The prognosis of the complications is the same as that of similar diseases arising under other conditions.

INTESTINAL SCHISTOSOMIASIS

The invasion stage in acute cases is similar to that of the urinary form. N. H. Fairley has shown that typical lateral-spined ova begin to be deposited in the sub-mucous coat of the rectum and sigmoid six weeks or more after infection, and diarrhœa or dysenteric symptoms appear in due course; the true nature of these can only be distinguished by finding the ova in the stools about forty or more days after infection. In nearly half of the infections no definite symptoms are present, and only microscopical examinations reveal the presence of the schistosome eggs. The bowel symptoms vary from simple or acute diarrhœa with some excess of mucus or a condition closely simulating membranous colitis, to chronic dysenteric symptoms with frequent stools and some tenesmus, with loss of weight and anæmia. In advanced cases tenesmus is greater owing to the presence of polypoid growths in the rectum; these may even protrude from the anus and resemble hæmorrhoids, and similar tumours higher up may reach a size allowing

of their palpation through the abdominal wall; they may even cause intestinal obstruction, as recorded in Egypt by Richards, Madden and Symmers, but such a condition does not appear to have been met with in South-American schistosomiasis. Perineal fistula may also occur, and much suffering or even fatal exhaustion may ultimately result. Appendicitis may result from the presence of numerous ova, with or without secondary bacterial infection.

The **complications** of this variety include **cirrhosis** of the liver, which may become cancerous, and a special form of **splenomegaly** found in Egypt by H. A. Day, who demonstrated the schistosome eggs in the fibrous tissue of the liver. In Nyasaland, W. H. Eye has reported a very similar condition, which often terminates fatally and resembles that found in Asiatic schistosomiasis, as described below. It has been suggested that these conditions are sometimes caused by the presence in the portal system of only male worms derived from the cercariæ of a single snail, so that no ova occur in the tissues or are passed in the evacuations. In these cases there is very great hard enlargement of the liver and spleen, producing a prominent abdomen, with diarrhœa, hæmatemesis, and irregular fever; the condition goes on to fatal cirrhosis, with fibrous shrunken liver, ascites and œdema. The lungs may be affected and show striation on X-ray examination.

Diagnosis. In this form the characteristic ova must be sought for in the stools or in rectal swabs. The search is facilitated by passing a suspension of a gramme of stool in water through a fine sieve or coarse cloth, and pipetting off the sediment of the filtrate after standing in a conical glass for microscopical examination.

ASIATIC SCHISTOSOMIASIS

The Far Eastern disease due to *S. japonicum* resembles the intestinal variety in its earlier stages, but the tendency to produce late enlargement of the liver and spleen, followed by progressive fatal cirrhosis of the former organ, is much greater. The ova have also been found in the brains of patients who had suffered from convulsions or paralysis. The disease was first recognised in this advanced stage, and was called Katayama disease on account of its prevalence in a district of Japan of that name; it has also been called Catto's schistosomiasis, after the discovery of its occurrence in Singapore by that worker. In Europeans infected while bathing in the Yangtse region of mid-China, the early symptoms in American sailors were found by Lambert and by Laning to commence in about two days with fever, malaise, abdominal pain, sickness and diarrhœa. These symptoms were followed by dermatitis or an urticarial rash with very large wheals up to 3 or 4 inches in diameter, which faded later, leaving red circular lines. Cough, with the occurrence of local patches of dullness and fine rales, indicate the involvement of the lungs. The blood shows a very high degree of

eosinophilia up to 60-80 per cent. In mild infections the worms may die and the patient recover within about a month, but in severe or repeated infections the disease passes on into the second stage of chronic dysentery, with some fever and tenesmus, and the appearance of ova in the fæces; there is also enlargement of the liver and spleen, which may last for several years. Ultimately the third stage of cirrhosis of the liver develops, with ascites, emaciation and irregular diarrhœa, with few or no ova in the stools. Appendicitis with ova in the tissues has been reported. Most cases of so-called Banti's disease in the Far East are due to *S. japonicum* according to H. E. M. Campbell. There are exacerbations in the summer months, when the worms are believed to produce most ova. This advanced stage eventually proves fatal, owing to the presence of incurable organic disease. Cerebral granulomata have been recorded in *S. japonicum* especially in China, with symptoms of drowsiness, coma and incontinence of urine and fæces, and later spasticity. Craniotomy followed by improvement is recorded in two cases.

Diagnosis. Schistosomiasis can only be recognised with certainty by finding the characteristic ova. In the intestinal and Asiatic varieties the ova are found in the fæces, most frequently in the mucus on the surface of formed stools, but in the late stage of hepatic cirrhosis the infection may sometimes have died out, so that the ova may no longer be found; *in such cases it is too late for treatment to be effective.* E. C. Faust and H. E. Meleny kept a concentrated emulsion of a stool, after sieving, for twelve hours in a conical flask; the hatched-out miracidia are found near the neck. Early diagnosis of the disease is of the greatest practical importance, as it may be possible to check its progress by destroying the parasites with antimony intravenously; the presence of a high degree of eosinophilia accompanying the symptoms already described should lead to repeated examination of the stools for the ova. This is especially important in all cases of diarrhœa or dysentery in the endemic areas of both forms of the disease, for there are no certain characters by which this variety of bowel trouble can be diagnosed clinically. If the true cause of the bowel disease is overlooked, the disease may progress to the incurable stage. In the late stage of enlarged liver and spleen, chronic malaria and kala-azar have to be differentiated from schistosomiasis in areas in which the former diseases are prevalent, as in some parts of China.

Prognosis. This depends entirely on the stage in which the disease is first recognised, and on proper treatment. Most cases of intestinal schistosomiasis respond readily to efficient antimony treatment if no great damage has already been done to the large bowel or liver. There is reason to hope that early *S. japonicum* infections may also yield to this method, although the evidence on the subject is still rather meagre. When serious hepatic cirrhosis has already developed, no treatment is of much avail, and terminal cancer of the liver is not very rare.

Treatment

Tartar Emetic. In 1917 Christopherson in the Anglo-Egyptian Sudan established the value of intravenous injections of tartar emetic in the treatment of schistosome infections. He found that ova in the urine became dark and no longer hatched out miracidia on the addition of warm water after a total dosage of 20–30 grains in three or four weeks. At the same time the symptoms of the infection other than those of an advanced organic nature disappeared due to the death of the adult *S. hæmatobium* and *S. mansoni*. The antimony treatment is also of value in early cases of *S. japonicum* infections provided cirrhosis of the liver and other serious organic disease have not already resulted.

Either potassium or sodium antimonyl tartrate may be given intravenously in ½ grain doses in a 1 per cent. solution gradually increased to 2–2·5 grains three times a week until the required result is obtained. In young children with small veins tartar emetic has also been administered by rectal injections of three grains in two ounces of water daily for a week. In Africa Alves and Blair have advocated intensive treatment by 1–2 grain doses of sodium antimonyl tartrate in 10 c.c. of 5 per cent. glucose solution injected intravenously very slowly thrice daily at three-hourly intervals for two days with a total dosage of 4–14 grains or approximately 1 grain per 12 lb. body-weight. After two months all the cases were freed from ova in the urine. Radioactive tartar emetic has been advocated and antimony sodium thioglycolate has also been given intravenously.

Fouadin is a less toxic antimony salt, ampoules of which can be injected intramuscularly, but it is rather painful and may produce severe vomiting. In adults doses of 1–4 c.c. are given on alternate days. It is also of value in early *S. japonicum* cases. Relapses may occur but in Porto Rico 78 per cent. of cures resulted.

Anthiomaline, or lithium antimony-thiomalate, is a soluble preparation of low toxicity, which can be given either intravenously or intramuscularly in a 6 per cent. solution in doses of 0·5–1 c.c. in children, and 1·5–4 c.c. in adults, every other day up to eight to ten injections. Quicker cures are reported with this drug than with tartar emetic.

Emetine has been found to be effective in schistosome infections by Diamantis and others, but on account of its greater cost it is chiefly used in children in whom intravenous medication is difficult. It is injected intramuscularly in similar doses to those advised in the section on amœbic dysentery. R. M. Gordon advises 1-grain doses of emetine periodide in milk three times a day for fifteen days to children, with results not much inferior to the daily injection of ½-grain doses of emetine hydrochloride, so that we have in emetine a useful alternative to the antimony salts in case of need.

Miracil D. Kikuth and Gonnert synthetised this valuable xanthoic compound and found it to be effective against schistosomes

in white mice and rhesus monkeys by oral administration. It produces transient toxæmia in the form of nausea and sickness, but is not cumulative. In *S. hæmatobium* and *S. mansoni* infections 0·2–0·3 gm. daily for six days a week for three weeks gave favourable results in Rhodesia with a few cures in cases followed up for sixteen weeks. Further trials are indicated as toxic effects are being reported.

Surgical measures on ordinary lines are required for the various organic complications of the genito-urinary system and the rectum. When extensive polypoid disease of the rectum remains after elimination of the worms and their ova by antimony treatment, the excision of from 9 to 17 inches of the mucous membrane of the rectum has been carried out with success by R. V. Dolbey and I. Fahmey in Egypt. The mucosa is removed from the anus upwards and the healthy mucosa is drawn down and sutured to the anus. A. G. Biggam advises diathermy with a special instrument for dealing at one sitting with a number of polypoid growths in the lower bowel.

Splenectomy has been used with case mortalities of 10–20 per cent. and usually without permanent benefit in view of more advanced liver infection being present in severe cases.

Prophylaxis. The simplest preventive measure is to avoid bathing or wading in infected waters ; sportsmen should be warned of the need to wear wading boots in the endemic areas of the disease, but in the case of the agricultural population this measure is not feasible. In Egypt it has been shown by R. T. Leiper that the *Bullinus* host of *S. hæmatobium* has a non-operculated shell, and so is very susceptible to drying for a few days. On his suggestion vast numbers of these dangerous snails have been killed by turning off the water in the irrigation canals for several days at a time, and in Iraq the snail carrier has been reduced greatly by cutting off the water for two weeks every three months, as reported by A. H. Hall. Where practicable the prevention of fæcal and urinary contamination of water is of great value, but its enforcement is very difficult among the backward indigenous races of the endemic areas. The Chinese method of sewage storage in cemented tanks destroys the ova. In the Sudan E. Pridie has reported that the provision of well-water, and deep latrines, and the employment of expert *Bullinus* hunters have proved of value in addition to periodic drying and chemical disinfection of canals. In South Africa F. Cawston advocates stocking infected waters with ducks and minnows, which feed on the carrier snails. In Egypt C. H. Barlow records material reduction in the snail carriers within one year by the inexpensive method of clearing weeds from the canals. *S. hæmatobium* infections are reported to have been eliminated from the Dakla Oasis in Egypt by persistent destruction of the *Bullinus* carriers in the canal waters by copper sulphate, and by tartar emetic injections of the affected patients.

The cercariæ in water will pass through ordinary sand-filters, but

Treatment

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The fish tapeworm does not occur in the tropics.

In *saginata* and *solium* infections eggs escaping from segments passed per anum are swallowed by the appropriate host, give rise to motile onchospheres which penetrate the gut and pass in the blood-stream to the muscles where they encyst to form cysticerci. Man is infected by consuming uncooked or insufficiently cooked flesh containing these encysted forms.

Tænia saginata. This is much the most frequently met with tapeworm in the tropics. The minute head is armed with suckers only. Length from 12 to 30 feet. The uterus has many fine lateral branches. *Cysticercus bovis* does not occur in man.

Tænia solium. The pork tapeworm is found much less seldom owing to the fact that many inhabitants of the tropics are forbidden to eat pork on religious grounds. The worm is only 6–9 feet in length. The lateral branches of the uterus are few and coarse.

The head has four suckers but has also a double row of hooklets round the anterior rostrum. The eggs—about 35 μ in diameter—have radially striated shells and are indistinguishable from those of the beef tapeworm. Unlike the beef tapeworm the egg of the pork tapeworm can develop in the human body giving rise to somatic tæniasis or cysticercosis.

The small heads of these tapeworms are seldom found in the stools and it is therefore important to be able to distinguish between the segments (proglottides) of the beef and pork tapeworms. For this purpose segments should be washed in water, pressed between two slides and held up to the light when the number and fine or coarse branching of the uterus will disclose the identity of the worm.

Beef and pork tapeworms do not give rise to symptoms, except psychological ones, but *T. solium* requires prompt expulsion on account of the danger that eggs may be ingested or that segments may be regurgitated into the stomach and there undergo digestion.

Treatment. This requires meticulous care in the preliminary preparation of the patient. Starve the patient—and the worm—for forty-eight hours. Hot water containing a little sodium bicarbonate may be allowed or weak tea without milk or sugar. At bedtime on the second day give 2 tablets of mepacrine. At dawn repeat the dose of mepacrine (200 mg.). An hour later give 2 gelatine capsules containing 15 minims each of recently prepared liquid extract of male fern—*Filix mas*. Repeat the dose of *Filix mas* every half hour till 120 minims have been given. One hour later give half an ounce of Sodium Sulphate in a small amount of hot water. Stools should be passed into a bedpan containing warm water so that no strain is thrown on the narrow neck of the worm. The stools should be carefully strained and examined for the head. *T. saginata* is more difficult to dislodge than is *T. solium* but scrupulous attention to detail will achieve success in a high proportion of cases. If the head is not found the treatment should not

they only live for about three or four days if they do not obtain access to a human or animal host, so storage of water soon removes them. The snails are also killed in forty-eight hours by 1 in 500,000 to 1 in 1,000,000 solutions of copper sulphate, which A. C. Chandler found to be the best of many disinfectants he tried. M. Khalil, in Egypt, found that 1 in 4,000,000 colloidal copper killed all molluscs in Nile waters, so that is also a valuable prophylactic measure. In South Rhodesia malachite (mineralised copper carbonate), finely ground, was found to yield an effective and cheap concentration of 0·5 parts of copper per million in natural waters. Under military conditions the entry of the cercariæ into the skin should be prevented by their destruction in water used for washing purposes by the addition of "caporit" (calcium *hypochlorite containing 70–75 per cent. of active chlorine), in a 0·1 gm.* tablet for a bucket or basin full of water. Bacteria are also killed by this strength. H. S. Blackmore advises 1 in 1,000,000 available chlorine for sterilising waters infected with cercariæ. Chloramine has also been found to kill cercariæ in filtered water in one hour in a dilution of 1 in 1,000,000.

OTHER HELMINTHIC DISEASES

Much ill health and disability is produced in warm climates by the heavy incidence of a variety of helminthic parasites due in the main to insanitary habits of poor or backward races. The most important on account of their wide prevalence and great pathogenicity are the ancylostomes, the schistosomes and several forms of filarial worms which have already been described.

Many of the less pathogenic helminths do not produce clear cut symptoms but certain stages of them are commonly found during naked eye or microscopical examination of human fæces, most frequently after the administration of anthelmintic drugs for hookworms.

Brief accounts of these human helminths of lesser import are therefore required to enable the practitioner in the tropics to recognise them when he comes across them and to carry out treatment required for their eradication from the system.

For details of their minute structure reference should be made to special works. Those with a world-wide distribution are described in textbooks of general medicine and require but brief mention for the sake of completeness.

CESTODES OR TAPEWORMS

There are three important tapeworms which pass their adult life in the human intestine :

Tænia saginata. The beef tapeworm.
Tænia solium. The pork tapeworm.
Diphyllobothrium latum. The fish tapeworm.

The fish tapeworm does not occur in the tropics.

In *saginata* and *solium* infections eggs escaping from segments passed per anum are swallowed by the appropriate host, give rise to motile onchospheres which penetrate the gut and pass in the blood-stream to the muscles where they encyst to form cysticerci. Man is infected by consuming uncooked or insufficiently cooked flesh containing these encysted forms.

Tænia saginata. This is much the most frequently met with tapeworm in the tropics. The minute head is armed with suckers only. Length from 12 to 30 feet. The uterus has many fine lateral branches. *Cysticercus bovis* does not occur in man.

Tænia solium. The pork tapeworm is found much less seldom owing to the fact that many inhabitants of the tropics are forbidden to eat pork on religious grounds. The worm is only 6–9 feet in length. The lateral branches of the uterus are few and coarse.

The head has four suckers but has also a double row of hooklets round the anterior rostrum. The eggs—about 35 μ in diameter—have radially striated shells and are indistinguishable from those of the beef tapeworm. Unlike the beef tapeworm the egg of the pork tapeworm can develop in the human body giving rise to somatic tæniasis or cysticercosis.

The small heads of these tapeworms are seldom found in the stools and it is therefore important to be able to distinguish between the segments (proglottides) of the beef and pork tapeworms. For this purpose segments should be washed in water, pressed between two slides and held up to the light when the number and fine or coarse branching of the uterus will disclose the identity of the worm.

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be repeated until segments again appear in the stool. Some clinicians administer an emulsion of male fern through a duodenal tube if recurrence occurs.

The above dosage is that employed for a healthy adult European male. It must be reduced for lightly built and debilitated persons. *Castor oil must not be used as a purgative* when using male fern as an anthelmintic.

The combination of carbon tetrachloride and oil of chenopodium used in the treatment of hookworm is sometimes effective in dislodging tapeworms.

Somatic Tæniasis or *Cysticercosis.* Epilepsy occurring for the first time in adult British soldiers was shown by MacArthur to be due to the presence in the cerebrum of dying cysticerci cellulosæ. Cysticerci may be found in all the muscles of the body with palpable cysts from the size of a pea to that of a large bean. A weedy-looking man may take on the appearance of a muscle bound professional " strong man " in a few weeks. It may be years before the cysts become opaque enough to be demonstrable by X-rays or to show up on radiography of the skull. A number of cases end up in mental hospitals. Treatment with antimony or other metallic poison may cause cysts to swell and cause dangerous *status epilepticus.*

Less Important Tapeworms

Hymenolepis nana—the dwarf tapeworm. This cestode which is believed to be identical with *H. fraterna* of the rat lives in the small intestine of the inhabitants of many warm countries being specially prevalent in Cuba and Sicily. The worm has no intermediate host. The larva enters a villus of the intestine, forms a cercocystis from which a fresh scolex appears. The adult worm is from ¼ to 2 inches in length. The head has a well marked rostellum with a single row of hooklets and there are four suckers. It may occur in very large numbers. Usually it produces no symptoms but in hyperinfestation there may be colic and diarrhœa. The eggs are oval, about 45 μ in diameter with two membranous linings containing an onchosphere with three pairs of hooklets.

Tetrachlorethylene as given for hookworm is probably the most reliable remedy. *Filix mas* does not produce expulsion.

Hymenolepis diminuta. A parasite of rats but is found in man in tropical Africa and in the West Indies. The worm is from 8 to 24 inches in length, there are suckers but no hooklets on the head. The circular egg is of a yellowish hue and is about 70 μ in diameter. The cysticercus stage occurs in the body cavity of insects. No symptoms are produced and *Filix mas* is an effective remedy.

Dipylidium caninum. A common parasite of cat, dog and jackal. It occasionally affects man. The cysticercoid stage is passed in the dog louse or flea. The worm, from 6 to 18 inches in length, has a character-

istic head with four rows of hooklets and four suckers. The round egg is 40 μ in diameter. Infection of man due to swallowing fleas produces no symptoms and the worm is susceptible to *Filix mas.*

Echinococcus granulosus. Tænia echinococcus. Hydatid. In this infection the adult worm is a parasite of the dog from which human infections are most commonly derived through close contact. It is an "occupational disease" of shepherds of Australia and Shetland. It is not uncommon in the tropics. The subject is dealt with in all standard textbooks of medicine and surgery. The Casoni intradermal test and a specific complement fixation test may aid the clinical diagnosis.

TREMATODES OR FLUKES

These worms are either leaf-like or cylindrical in shape and are found only in vertebrates. The most important members of this group are the schistosomes.

Except in the case of the schistosomes they are hermaphrodite. The human species are characterised by an oral and a ventral sucker by means of which they attach themselves to their hosts. They have complicated life histories in which a mollusc, which the larvæ reach through water, plays an important part.

Fasciola Hepatica. This liver fluke has been found in man only a few times but is very common in cattle, sheep and goats in which it produces liver rot. It has a wide distribution including India.

It is leaf shaped, about 1 inch long and its cuticle shows many minute spines. Anteriorly the body is prolonged to form a cone behind which it broadens to form shoulders between which a large muscular ventral sucker is situated.

Life History. After passage of the eggs by the vertebrate host a ciliated miracidium develops and escapes into water to infect a snail. *Limnæa truncatula*, in which first sporocysts, then rediæ, and later tailed cercariæ develop. The cercariæ leave the water and encyst on blades of grass whence on ingestion they reach their adult *habitat*—the bile ducts.

Pathogenicity. Cyst-like dilatations of the bile ducts occur and if the infection is a heavy one jaundice, toxæmia and cirrhosis of the liver may result. Brown ovoid operculated eggs 140 by 90 μ may be found in the fæces.

Treatment is unsatisfactory but heavy doses of emetine may be beneficial.

Fasciolopsis Buskii. This is the largest of the trematode parasites of man with an average length of 30 mm. It is flesh coloured and is oval in shape. It is normally a parasite of the pig. It is common in China, Siam and Assam.

The eggs, which are indistinguishable from those of *F. hepatica* mentioned above, hatch out miracidia after being some days in water.

These bore their way into snails, chiefly those of the *Planorbis genus*. From these, cercariæ emerge and encyst on various water plants. The ingestion of these contaminated plants results in development of the adult form in the intestinal canal sometimes in very large numbers.

Pathogenicity. Heavy infections produce diarrhœa, ascites and general œdema.

Treatment. Carbon tetrachloride or tetrachlorethylene as given for hookworm infection rid the patient of his parasites.

Clonorchis Sinensis. This fluke is widely distributed in China, especially in the Southern provinces, in Japan, Korea, Indo-China and India. It inhabits the bile ducts of man, cats and dogs. It is a flat leaf-shaped worm, about 1 cm. in length and of reddish brown appearance. The eggs may be found in the stools as operculated flask-shaped yellow ova measuring 30 by 15 μ but they are indistinguishable from those of the very small fluke *Heterophyes heterophyes.* They contain a ciliated miracidium which escapes in water and infects small snails of the *Bithynia genus* in the tissues of which sporocysts and cercariæ develop. These cercariæ in their turn develop in certain fresh water fish which feed on the infected snails. Man is infected by consuming such fish raw or insufficiently cooked. The adult flukes reach the bile ducts *viâ* the duodenum and attain maturity there.

Pathogenicity. When the parasites are present in large numbers the bile ducts become thickened to form cyst-like cavities and the liver enlarges. Jaundice and ascites may develop. The nature of the affection can be recognised by finding the ova in the stools.

Treatment. At present this is unsatisfactory. Continuous non-surgical drainage of the biliary tract using a duodenal tube and concentrated sodium sulphate combined with the use of gentian violet by mouth may be tried. Crystal violet (B.P.) may be given in a dosage of 18 mg. per kilo for ten to twenty days.

Paragonimus Westermanii. This fluke otherwise known as *P. ringeri* is found in China, Korea and Japan. The adult worms have been met with in man, dog, cat, pig, tiger and wolf. The lungs are chiefly infected and less commonly the liver, spleen and other organs of the body.

Character. The flukes are reddish-brown in colour and shaped like one half of a pea. In size thay are 10–20 mm. by 5–10 mm. The eggs are most commonly found in the sputum and occasionally in the fæces. They are brown, operculated oval bodies measuring 70 by 45 μ and contain an unsegmented ovum.

Life History. In water the eggs develop a miracidium which enters the fresh water snail *Melania libertina* in which rediæ and then cercariæ are formed. Escaping from their mollusc host these cercariæ infect fresh-water crabs and crayfish through eating which in an uncooked condition man falls a victim. The parasite migrates from the intestine to reach the lungs.

Pathogenicity. The presence of this parasite in the lungs gives rise to the condition known as endemic hæmoptysis. The onset is insidious with persistent cough accompanied by rusty brown sputum in which the characteristic ova may be found. Attacks of hæmoptysis may occur at times and lead to an incorrect diagnosis of pulmonary tuberculosis if microscopic examination of the sputum is neglected. Invasion of other parts of the body by the worms may cause dull abdominal pain and diarrhœa or Jacksonian epilepsy and other nervous symptoms due to invasion of the central nervous system. General lymphadenitis may develop, most commonly involving the axillary and inguinal glands. Superficial ulceration may occur. When any of these symptoms are met with in the endemic area of the disease search should be made for the ova in the sputum and stools to allow a correct diagnosis to be made without delay. Post-mortem the lungs may reveal cysts somewhat resembling tuberculous lesions together with abscesses, dilatation of bronchi and localised cirrhotic changes.

Treatment. Emetine and sulphonamides have been tried in large doses and improvement has been reported but on the whole treatment is unsatisfactory and, as is the case with all fluke infections, prevention is better than cure.

NEMATODES

Much the most important of this class of human helminths are the strongyloidea, ancylostoma and necator which are dealt with at length in Chapter XIX and the filaridæ for a description of which see Chapter XX. The following which are of much less pathological and clinical importance are dealt with briefly below.

Ascaris Lumbricoides. The round worm. This familiar worm is common in warm climates as in the world in general. It is commonly found when an anthelmintic has been used for the expulsion of hookworms and it requires no special description here. Its eggs are easily distinguished when examining stools by their brown colour, rounded or broadly oval shape measuring about 60 μ by 45 μ and by their fæcally stained outer coat with irregular thickenings. Freshly passed eggs show no development of the contained ova but development of the larval form takes place in a few weeks. They can then infect man on being swallowed on uncooked vegetables.

Pathogenicity. This is slight unless the worms are present in large numbers but in the tropics the round worm must always be thought of as a possible cause of symptoms of intestinal obstruction, bile duct obstruction and of pain in the appendix region. Further in debilitating disease wandering round worms may get into the larynx and cause death.

Treatment. The classical treatment is Santonin followed by a purge. For adults 3–5 grains of santonin may be administered followed in two hours by a saline purge. Nowadays it is more usual to use the

chenopodium and carbon tetrachloride treatment as recommended for hookworm as in the tropics both infections usually occur in the same patient.

Enterobius Vermicularis. The threadworm or pinworm. This is another familiar worm of world-wide distribution. Pruritus ani is the presenting symptom. The worm is white and threadlike. It can readily be distinguished from the hookworm by the cuticular expansion or halo round the mouth and by the absence of the prominent teeth or cutting plates of the hookworm.

Characters. The female threadworm measures 1 cm. in length and has a long tapering pointed tail. The male is only 4 mm. in length and its posterior extremity is curved. The ova are oval and colourless measuring 55 μ by 25 μ. They contain a more or less fully developed embryo. *The eggs are deposited by the female worms outside the anus* in the natal folds. The eggs are conveyed to the mouth by finger nails infected whilst scratching. The embryo hatches in the stomach.

After two moults the worm reaches the large intestine and assumes its adult form.

Diagnosis. The eggs are not found in the fæces. A cellophane swab should be rubbed over the perianal region and over the lower portion of the anal canal. The eggs are then easy to demonstrate under a microscope. The first essential in treatment is to prevent re-infection by the imposition of rigid methods of personal hygiene. The finger nails should be cut short, the scrubbing brush must be employed at frequent intervals, the perianal region should be smeared with dilute ammoniated mercury ointment. Retention enemata of Infusion of Quassia or of Hexylresorcinol 1 : 2,000 after a soap and water enema may be employed once a fortnight.

Gentian violet may be given in enteric coated pills 1 grain t.d.s. before meals for a fortnight.

Phenothiazine may be given to adults 75–90 grains daily for not more than a week.

Trichuris Trichiura. Trichocephalus dispar or whipworm. This worm has a world-wide distribution ; identical worms exist in the cæca of herbivorous animals.

Description. It is easily recognised by the fact that three-fifths of its length of 4 to 5 cm. consists of a very thin whip-like portion and that its terminal two-thirds is thicker with a breadth of 2 mm. Its eggs are equally characteristic with their long oval shape measuring 30 by 25 μ. with a thick brown outer coating with a rounded knob at either pole. They are found mostly in the cæcum with their thin anterior ends embedded in the mucous membrane. Their pathogenicity is slight or nil although appendicitis had been attributed to their action. The eggs are unsegmented and the embryo develops slowly. Development is direct from the ingestion of stale fæces. The embryo

escapes in the stomach when the egg is swallowed and makes its way to the cæcum.

Treatment. Oil of chenopodium with carbon tetrachloride, or hexylresorcinol as given for hookworms are successful in removing a proportion of the worms but the treatment has to be repeated as a rule.

Trichinella Spiralis. Trichina spiralis. This worm has a general distribution but is not common in the tropics where pork is a rather rare article of diet. The adult parasites are very common in the small intestine of rats. The females are viviparous and the embryos voided by the female invade the intestinal wall and make their way to the muscles where they encyst. Consumption of insufficiently cooked parasitised flesh of the pig is the source of infection in man. Outbreaks have been reported from Africa, India and China. Minor degrees of trichinosis are probably much more common than is usually supposed; in cases of muscle pain with fever and eosinophilia the diagnosis of trichinosis should be considered.

Strongyloides Stercoralis. This nematode is common in tropical countries especially those with a damp climate such as Brazil, Cochin China and Malaya. It may be present in large numbers in the jejunum. These small nematode worms are not readily demonstrable. They are hardly visible to the naked eye but may be seen on microscoping a scraping from the intestinal mucosa in which they become buried. The parasitic female measures about 0·5 mm. in length and in the posterior portion are some 50 eggs in a row nearly the diameter of the worm.

The eggs contain developed larvæ which are found moving in freshly passed stools. They gain access to man by penetrating unbroken skin as in the case of ancylostomes. A stage is passed in the lung capillaries.

Pathogenicity. When present in large numbers this minute worm may cause troublesome diarrhœa. Blood and mucus may appear in the stools. A rash may appear at the places where the larvæ penetrate the skin.

Treatment. Treatment is unsatisfactory at present although gentian violet in 1 grain doses in enteric coated pills given t.d.s. for three days has been used extensively.

PRESERVATION OF HELMINTHS

To the practitioner in the tropics the following methods of preserving helminths for more minute examination by specialists may be of use :—

Cestodes. Tapeworms relàx and their heads become detached from the intestinal mucous membrane in fresh water. They should be preserved in ten times their volume of 3 per cent. formaline.

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CHAPTER XXII

POISONOUS SNAKES, SCORPIONS AND VENOMOUS SPIDERS

CLASSIFICATION AND IDENTIFICATION OF SNAKES

Harmless snakes include two families of small, blind, worm-like snakes living underground. Identical small scales cover both back and belly. Large ventral scales are absent.

Five families are characterised by having narrow transverse ventral plates or scales, which do not extend completely across the belly, and many small costal scales visible on each side of the large ventral ones.

Colubridæ. This large class of snakes includes harmless and poisonous varieties, the latter are differentiated by anteriorly placed fangs in the upper jaw. (1) **Aglypha** with total absence of anything resembling a poison fang. (2) **Opisthoglypha** have imperfectly grooved hindermost teeth in the upper jaw, which are not effective as poison fangs. Alcock and Rogers showed that the parotid glands of some of them contained enough poison to kill small animals on injection, but they are not dangerous to man, being thus intermediate between the harmless and the poisonous snakes. (3) **Proteroglypha** with a specialised fang on each upper jaw replacing the outer row of teeth of non-poisonous varieties. These constitute the poisonous colubride snakes. The *colubridæ* have large ventral scales extending almost completely across the belly. Among the more important poisonous snakes are the following :—

Hydrophidæ or Sea Snakes. These can be distinguished at a glance by having tails flattened vertically to allow of rapid swimming. They are all poisonous, although fresh-water snakes are not so. Their heads are covered with large plate-like shields. Numerous species are met with in tropical seas. On the coasts of India *Enhydrina* and *Platurus* are the more deadly because of their large heads and the amount of venom they emit on biting. Most of the *Hydrophidæ*, on the other hand, have such small heads that it is difficult for them effectually to bite human beings and they eject very small amounts of venoms. The venoms of sea snakes were found by Rogers to be especially lethal to cold-blooded animals, such as fish and differ in this respect from the venoms of land snakes.

Cobras are deadly snakes widely distributed in the Eastern Hemisphere. Only one genus of coral snakes occurs in the Western Hemisphere. Cobras can be distinguished from all other snakes by having a third supralabial shield, which touches the nasal and eye shields. The characteristic expanding hood of a rampant cobra is not evident after death. They are widely distributed in Asia and Africa.

Trematodes should be well washed in water and also preserved in 3 per cent. formaline.

Nematodes including round worms should be washed in normal saline, killed by placing them for about a minute in hot water at 70° C. or in 3 per cent. hot formaline. They should then be preserved in 70 per cent. alcohol. To examine the smaller nematodes for structure under a low power microscope clarify them for a short time in liquefied carbolic acid.

LEONARD ROGERS

In Africa true vipers are represented by the African puff adder, *Bitis arietans*, the horned viper of Egypt, *Cerates cornatus*, the Gaboon viper, *Bitis gabonica* ; all very deadly snakes.

Crotalinæ, or pit vipers are especially numerous and deadly in America. Those of Asia and Australia are mostly less dangerous. They are distinguished by a loreal pit near each eye of unknown function.

In India thirteen species have been described by Wall, mostly not exceeding 2 or 3 feet in length and their bites are rarely fatal to man, although they produce severe local symptoms.

American species include such deadly snakes as the rattlesnake, *Crotalus horridus*, the copperhead, *Ancistrodon contortrix*, the moccasin, *Ancistrodon lanceolata*, which constitute a formidable group.

Classification of Physiological and Pathological Properties of the Venoms. Boquet summarises the actions of different classes of snake venoms thus : (1) Curarising anticoagulants, including the *colubridæ* of Asia and Africa and some of those of Australia. (2) Curarising coagulants, including Australian *colubridæ*. (3) Hæmorrhagic anticoagulants, which include the viperines of Africa and America. (4) Hæmorrhagic anticoagulants, including the viperines of Europe, America, Asia and the genera of *Echis* and *Cerastes* of Africa.

Toxic Action. The colubrine snakes as a class cause death in a totally different manner from the viperines, as illustrated by the following table, showing the action of the poisons of each class on the nervous system and the blood.

THE TOXIC ACTION OF SNAKE VENOMS

Class	On Nervous System	On the Blood and Blood Vessels		
		Hæmolysis	Coagulation	Hæmorrhages
Hydrophidæ (Sea snakes).	Paralysis of respiration and of muscles.	Very slight.	Slight reduction.	*Nil.*
Colubridæ.	do.	Moderate.	*Nil.*	*Nil.*
Viperinæ (true vipers).	Paralysis of vasomotor centre in medulla.	Pronounced.	Intravascular clotting, followed by incoagulability.	Pronounced.
Crotalinæ (pit vipers).	do.	do.	do., but less pronounced. Incoagulability pronounced.	Very pronounced.

The main investigations by which the actions of the two great classes of snake venoms were established are very briefly as follows. In 1873 Lauder Brunton and Fayrer found that cobra venom killed animals through paralysing the respiratory centre in the medulla, and also the muscle end plates, especially of the diaphragm, and in 1873–74

In the latter are found the spitting cobra *Naia nigrifolis*, and mambas or tree-cobras. In India the following two are very deadly.

Naia naia, or common cobra, is the most widespread. It may reach a length of 6 feet, its colour is variable and many show a spectacle-like marking on the hood. The *Hamadryad* or king cobra, can be distinguished from all other snakes by having a pair of large shields behind the parietals on the dorsal aspect of the head. It is the largest of Indian poisonous snakes, measuring up to 15 feet in length. Owing to the large amount of venom it ejects it is very deadly; it is most common in Burma.

Indian Coral Snakes are mostly about 2 feet in length and so are presumably not very poisonous, but they do not appear to have been closely investigated. Coral snakes also occur in America.

Bungarus coeruleus, or the common krait, is very deadly, although rarely more than 4 feet in length. It has a light coloured belly and pairs of light arches across its back. **Bungarus fasciatus** or branded krait, is easily distinguished by having alternate wide yellow and black bands across its back and by characteristic large central dorsal scales. It may measure up to 6 or 7 feet in length, but is less dangerous than the smaller common krait because its venom is weight for weight less toxic.

In Australia the above classes of snakes are represented by the death adder, *Acanthophis antarcticus*, the tiger snake, *Notechis scutatus* and the black snake or *Pseudechis porphyriacus*.

Viperidæ constitute the other great class of poisonous snakes. They require to be carefully distinguished from the *Proteroglypha* because the difference in the action of their venoms necessitates different treatment. They include the true vipers and the pit vipers and predominate in the Western Hemisphere. They all have broadly arrow shaped heads and a very large fang on either side of the upper jaw, which is folded back against the roof of the mouth when not in action. They are divided into the two following classes.

Viperinæ or vipers, characterised by their snout and the crown of the head being covered with small scales similar to those on the back and sides of their bodies and the absence of the loreal pit of the pit vipers. They are much more numerous in the Western than in the Eastern Hemisphere.

Indian species include (*a*) *Vipera russelli*, or *Daboia russelli*, is light brown in colour with three longitudinal series of large spots on the back and dark marks on the head. It rarely exceeds 5 feet in length and its bite is frequently fatal to man. It is prevalent all over India south of the Ganges and in Burma and Ceylon. (*b*) *Echis carinata*, or Phoorsa, is chiefly met with in areas with sandy soil south of the Ganges and in North-West India. Undivided shields beneath the tail distinguish it from other snakes of this class. It rarely exceeds 2 feet in length and is not as dangerous as Russell's viper.

vipers as a whole. In addition, there is a hæmorrhagic effect which is most marked in the case of the rattlesnakes. This is due to the action of a hæmorrhagin in destroying the endothelial lining of the smaller blood vessels.

The essential difference in the toxic action of the two classes of venoms can be observed in pigeons injected with lethal doses, for, with poisons of the *Hydrophidæ* or *Elapidæ*, the respirations become steadily slower and more feeble until they cease, but the blood pressure is maintained, and a temporary asphyxial rise occurs with the failure of respiration. This is followed by secondary cardiac failure. With small slowly-acting doses a general paralysis also occurs, but this may be recovered from completely in twenty-four hours if complete respiratory

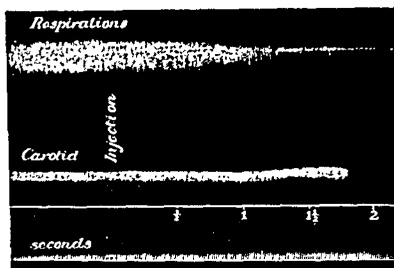


FIG. 77. Blood pressure and respiratory tracings showing death by respiratory paralysis due to Colubrine snake poisoning (*Hamadryad* or king cobra (L. Rogers)). (From Philosophical Translations of Royal Society of London.)

paralysis is avoided by keeping just within the lethal dose. By fractionation methods the neurotoxic and hæmolytic constituents of cobra venom have been separated and their actions tested. The results confirm that the essential cause of death is respiratory paralysis due to the neurotoxic fraction. With a large dose of Russell's-viper venom the pigeon dies of convulsions in a minute or two, and the venous blood in the systemic and portal veins, and in the pulmonary arteries, is found clotted solid after death. But this is rarely, if ever, found in fatal viperine poisoning in man, because the relatively smaller dose which is injected subcutaneously by the snake causes a loss of coagulability and hæmorrhages in cases of long survival, while large doses cause a fatal failure of the circulation due to vasomotor paralysis. The minor importance of the blood changes except in rapid death after very large doses is confirmed by the finding of J. Taylor (1935) that Daboia venom loses nothing of its toxicity after the hæmorrhagic factor has been

they demonstrated that the circulation could be maintained for many hours when artificial respiration was kept up, but recovery of the respiratory centre did not take place. Work on Australian colubrine snake venoms by C. H. Kellaway indicated a curare-like paralysis of the respiratory muscles as the cause of death rather than paralysis of the respiratory centre ; for with capacity amplifiers he demonstrated motor impulses descending the phrenic nerve after failure of respiration in small mammals. In the case of large doses of Indian colubrine venoms, on the other hand, L. Rogers in 1903, confirmed by recent work in India by K. Venkatachalam, showed that large and rapidly fatal doses might cause death from respiratory failure, yet stimulation of the phrenic nerve showed that the diaphragm was still unparalysed, although with smaller and slowly acting doses paralysis of the diaphragm might be demonstrated immediately after death from respiratory failure. In 1890 Weir Mitchell and Reichert showed that *the main lethal action of the rattlesnakes was due to loss of coagulability* of the blood and hæmorrhages, and later Flexner, Noguchi and others described hæmorrhagin, hæmolysin and neurotoxins in this venom. In 1895 C. J. Martin found that the Australian Colubrine *Pseudechis porphyriacus* produced intravascular clotting as well as respiratory paralysis, and he suggested that the Indian Russell's viper caused fatal convulsions in the same way. Lamb, in 1902 in Bombay, confirmed this, and found intravascular clotting in the veins to be the ordinary cause of death in small animals injected with lethal doses of the venom of Russell's viper. L. Rogers in 1903–04 recorded comprehensive blood-pressure and respiratory tracings of the action of the venoms of all four main classes of snake venoms from three continents. These established, in the first place, that the venoms of four genera of *Hydrophidæ*, of the king cobra, and of both Indian kraits killed by producing respiratory and more or less muscular paralysis as with *cobra venom, but the banded krait resembled the Australian Pseudechis* in also causing a great fall of blood pressure due to viperine-like poison. Secondly, he demonstrated that a small dose of Russell's-viper venom, injected intravenously, could kill by a rapid fall of the blood pressure without any intravascular clotting, but with a loss of coagulability. This condition could always be produced by injecting a sub-lethal dose to cause loss of coagulability, followed by a large lethal dose causing fatal circulatory failure. He proved, by cutting the spinal cord, and by direct observations on the portal circulation, that the essential cause of death was paralysis of the medullary vasomotor centre, the heart continuing to beat to the end. R. N. Chopra and J. S. Chowhan confirmed this finding by showing that clamping of the mesenteric arteries before the injection of a large dose of Daboia venom prevented the rapid fall of blood pressure. Moreover, the African puff adder, the American rattlesnake, and the Indian pit vipers, all caused death in the same manner, so that vasomotor paralysis is the main action of the

vipers as a whole. In addition, there is a hæmorrhagic effect which is most marked in the case of the rattlesnakes. This is due to the action of a hæmorrhagin in destroying the endothelial lining of the smaller blood vessels.

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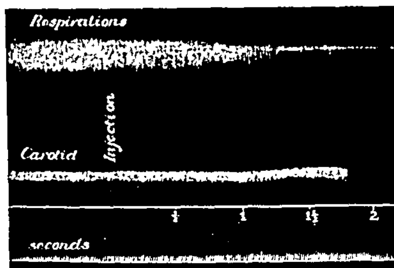


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neutralised. The two modes of death are illustrated by charts, which show the action of the venoms of the *Hamadryad*, or king cobra, and of the African puff adder (*see* Figs. 77 and 78).

The *Echis carinata* is the next most important Indian viper, but its venom is less toxic than that of the Daboia. R. N. Chopra found the coagulant factor weaker, but the hæmorrhagins ten times as strong as those of the Daboia, causing extravasation of sero-sanguineous fluid with a tendency to bleeding from mucous membranes and local gangrene. Nine of seventeen American snake venoms were found by H. Eagle capable of coagulating citrated blood or plasma, in the case of seven through converting fibrinogen into an insoluble fibrin-like modification, and in addition three of these converted prothrombin into thrombin while two had the latter action only. They included

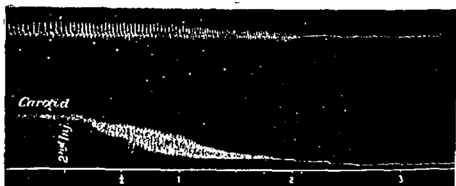


Fig. 78. Blood pressure and respiratory tracings showing death by vasomotor paralysis due to viperine snake poisoning (African puff adder (L. Rogers)). (From Philosophical Translations of Royal Society of London.)

three varieties of Bothrops and four of Crotalus. The deadly Fer de Lance (*Bothrops atrox*) venom was active in a dilution of 1 in 25 *million.*

Symptoms and Diagnosis of Snake Poisoning

On a patient being brought for treatment for snake bite, inquiries should first be made whether the snake was seen or killed and identified. If the snake is available an examination of its mouth for the typical poison fangs anteriorly in the upper-jaw will reveal if it is a poisonous one, and examination of the head will show at a glance whether this has the arrow shape of the viper's head or not. If the snake is found to be non-poisonous the patient may still be suffering from acute, and even fatal, shock due to fright, but an assurance that the bite was not dangerous, and simple treatment for shock, will nearly always rapidly allay the symptoms which appear much sooner than do those due to snake venoms.

If the snake has not been accurately observed or killed, the site of the bite should be closely examined for signs of the typical two

punctures of the fangs a short distance apart, but it should be remembered that occasionally only one fang may have penetrated the skin, in which case the dose injected is likely to be a small one. Puncture marks made by the fine needle-like fangs of such colubrines as cobras and kraits are very small and difficult to locate as compared with those made by the large fangs of vipers. If some time has elapsed after the bite, local swelling due to hæmorrhagic effusion will be present, and this is likely to be greater in viperine than in colubrine venoms, but on incising the site some effusion will be evident within a very few minutes with either class of venom. In any case treatment should be applied at once without waiting for symptoms of poisoning to appear, as by delay the chance of saving the patient is likely to be lost. The first symptoms appear after from fifteen minutes to several hours in accordance with the amount of venom injected. Nausea or sickness, faintness, rapid soft pulse and slowing of respiration are prominent symptoms.

If the patient is first seen an hour or more after being bitten the respirations should be carefully noted, and, if they are becoming slow and shallow, while the pulse is not seriously affected, the case is a dangerous one of colubrine poisoning, and some of the venom has already become fixed in the central nervous system. Weakness due to steadily increasing muscular paralysis ensues in patients who live for some hours. On the other hand, if the respirations are normal but the pulse is very feeble and the blood pressure extremely low, apart from mere fright, the case is nearly certain to be one of viperine poisoning. In this case confirmatory evidence will be found in the extensive hæmorrhagic effusion at the site of the bite, and especially in the oozing of incoagulable blood from the fang marks, which is pathognomonic of viperine poisoning. If the patient has survived for a number of hours, septic inflammatory processes are likely to be present, and are a source of great danger, as in viperine poisoning death often occurs after two or more days from this complication.

Prognosis. This depends essentially on the amount of venom which the particular snake introduces when biting, and on the toxicity of the venom. In both of these respects there are great differences in various species. For example, L. Rogers, in 1903, found that, although sea-snake venoms are ten times as deadly as that of the cobra, most of the sea snakes eject too small a dose to kill a man, but he confirmed D. D. Cunningham's estimate that both king cobras and cobras commonly eject ten times the lethal dose for a man, hence the deadliness of their bites. On the other hand, the Russell's-viper venom is several times weaker than that of the cobra, and the former ejects only from one to two lethal doses for an adult man, so its bites are less deadly. More recently H. W. Acton and R. Knowles arrived at very similar conclusions by a different method. They also found that the *Echis carinata* ejects only about two lethal doses, the kraits four to five, while

neutralised. The two modes of death are illustrated by charts, which show the action of the venoms of the *Hamadryad*, or king cobra, and of the African puff adder (*see* Figs. 77 and 78).

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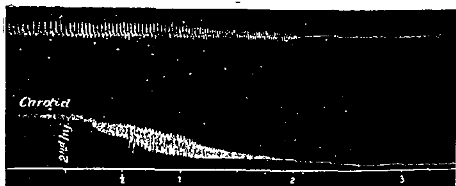


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M. L. Ahuja found that antivenenes prepared from the venoms of Indian and South African cobras neutralised both venoms. C. H. Kellaway and F. Eleanor found marked cross protection with the antivenenes prepared from the tiger snake and the copper-head respectively.

Anti-cobra serum is quite inert against the venoms of viperine snakes, but an antivenene against Russell's-viper venom has been prepared in India by Lamb and his successors, and is issued combined with antivenene against cobra venom, so as to be of value against both classes of poisonous snakes. Acton and Knowles, however, came to the conclusion that it should be concentrated to ten times its present strength if it is to be really effectual in most cases of snake bite, but here again 100 c.c. of the combined antivenene should be injected intravenously whenever it is available in the hope that the dose of venom actually received by the patient is only slightly above the minimal lethal dose. Detoxication of venoms used for making antivenenes by incubating with formalin at 37° C. has been successfully used in South Africa and in India. The subcutaneous or intramuscular injection of antivenene is of little value, because its much larger molecular weight makes its absorption slower than that of the venom. Acton and Knowles concluded that twice as much is needed when given intramuscularly and four times as much subcutaneously to neutralise a given quantity of venom, as compared with the dose given intravenously. Antivenene should also be injected locally to neutralise the venom at the site of the bite. In South America antivenenes have been found to lose 50 per cent. of activity in the first few years and then remain constant for twenty-five years.

Destruction of the Venom at the Site of its Injection. From what has already been said concerning the uncertainty of the antivenene treatment, even if the requisite doses and apparatus for intravenous injection are available on the spot, it is clear that a far more practical treatment would be some method of destroying the poison at the site of its injection before a lethal dose has been absorbed into the circulation. Moreover, if less than a fatal dose has been absorbed before the patient comes under medical treatment, the destruction of the greater part of the remaining unabsorbed venom may turn the scale in his favour. It is also clear that the available antivenene may be enough to neutralise the smaller total dose of venom which will be absorbed when local measures are adopted, while it might have been far too small to neutralise the whole dose if none is destroyed locally. Here again the method of choice depends on the circumstances, for if the patient is brought promptly to a hospital or dispensary, where syringes and solutions are ready for use, chemical antidotes can be injected with benefit at and around the site of the bite to destroy the venom locally. Unfortunately, cases of snake-bite usually occur when the victim is far from such aid ; it was for such contingencies that Sir

the Indian pit vipers do not eject even one fatal dose, which explains their well-known comparative harmlessness. On the other hand, the large pit vipers of America eject greater amounts of venom, and are consequently very deadly.

Moreover, it is fortunate that the deadly cobra can only strike downwards ; also its fangs are smaller and its mouth does not open so widely as that of the viper, hence it cannot strike home so effectively when it bites a flat surface or a large limb, so the full dose is only injected when it bites such parts as a finger or toe. If the full dose of the poison were always injected, recovery would scarcely ever occur after the bite of a cobra. As it is impossible to tell in any individual case what dose has been injected into the tissues, remedial measures should always be applied vigorously and patiently in the hope that only a moderate dose of venom has been received by the patient, as in that case the excess of the poison over the lethal dose may be dealt with successfully and recovery may result.

Treatment

Specific Treatment with Antivenene. Calmette first demonstrated that an antitoxic serum against cobra venom could be made by repeated injections of gradually increasing quantities of venom into horses, and Fraser in Edinburgh soon after arrived at a similar conclusion. C. J. Martin found that anti-cobra serum was not specific against the Australian colubrine snakes. L. Rogers found that anti-cobra serum supplied by Calmette had some power of neutralising the venoms of the sea snakes, king cobra, and the common krait, but not that of the banded krait, which has a partially viperine action. Proportionately larger doses were required when dealing with other colubrine snakes than in the case of the cobra itself. From the quantities of venom which he obtained from different freshly-caught snakes, and the neutralising power of the antivenene against each, he estimated that over 400 c.c. of Calmette's anti-cobra serum was required to neutralise the amount of venom ejected at a bite by the cobra, and of the *Enhydrina*, one of the most deadly of the sea snakes, but 600–800 c.c. in the case of the common krait and the king cobra, and then only if the doses were injected intravenously. Acton and Knowles estimated that in patients dying of cobra bite within two hours or less after the bite, over 700 c.c. of antivenene, which is in excess of a sub-minimal lethal dose of serum, would be required to neutralise the venom so as to save the patient, while 50–100 c.c. might suffice to save patients who would not die until two to six hours after the bite. Still smaller quantities may save those who have received doses of poison which are only slightly in excess of the minimal lethal dose. In view of the uncertainty regarding the dose of venom which has been received, it is wiser to inject 100 c.c. of the serum intravenously in all colubrine poisoning cases when possible.

strength of 1 in 12 can be kept in hermetically sealed amber-coloured glass tubes in a dark, cool place for several months without losing much of its efficacy.



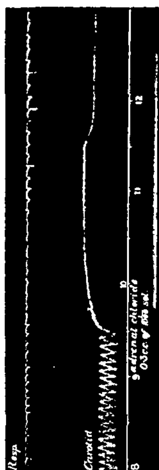


FIG. 79. Blood pressure and respiratory tracings showing vasomotor paralysis due to rattlesnake venom counteracted by adrenaline (L. Rogers). (From Philosophical Translations of Royal Society of London.)

Ligature. When any snake has bitten a person on one of the extremities, the first action should be the prompt application of a ligature. An elastic ligature, such as a piece of rubber tubing or the inner tube of a bicycle tyre, is far more effective than an inelastic ligature, but as a rule there is no choice, and the first thing that comes

Lauder Brunton invented his convenient little snake-bite lancet, with a protected blade at one end, and a receptacle at the other containing crystals of **permanganate of potassium**, which has long been known to destroy the albuminous snake venoms by oxidising them into harmless substances. The passage of the first Anti-vivisection Act in 1876 stopped the experiments which were being carried out by Brunton and Fayrer, and so they were unable to secure proof of the value of this method of treatment. It was nearly thirty years later, in 1903, that L. Rogers, at Brunton's request, carried out tests which proved that three to five times a lethal dose of venom of either the cobra or Russell's viper could be reduced below a lethal dose under the following conditions : The venom was injected into the leg of a cat, a ligature was applied within five to ten minutes, an incision made, and permanganate crystals with a little water were rubbed in at the site of the injection, and recovery took place. With large doses of cobra venom, success was not obtained after the lapse of more than ten minutes. In 1905, the same worker recorded twelve cases of bites by poisonous snakes treated by this plan with ten recoveries ; the failures occurred in persons who came several hours after being bitten. Admitting that a few of the patients may not have received a fatal dose, there can be little doubt that some lives were saved. Acton and Knowles later came to the conclusion, from animal experiments, that a solution of permanganate injected at and around the site of the bite, and massage applied to distribute it, is more effective than the method of incision with rubbing in of the crystals, so when a syringe is at hand this plan may be used. In cases of acute conjunctivitis, produced by such spitting snakes as *Naia nigricollis* of North-west Africa, washing out with 1 in 5,000 potassium permanganate and the instillation of atropine should be used.

In Australia S. Pern has treated about a dozen cases of snake-bite in men, and five in dogs, by the injection under and around the punctures of the fangs of several syringefuls of as strong a solution of permanganate of potash as can be made in cold water. All of them recovered without any harmful results.

Chloride of gold solutions were advocated over four decades ago by D. D. Cunningham, and later by Calmette. Acton and Knowles advised the use of this chemical in 10–20 c.c. doses of a 1 or 5 per cent. solution injected at and immediately around the site of the bite. Chemicals such as permanganates and gold chloride should not be injected intravenously, as they are both poisonous and ineffective by that method. Locally, they destroy the tissues as well as the venoms, and small sloughing wounds result from rubbing in permanganate crystals, while extensive necrosis is likely to occur after injections of chloride of gold. Calmette recommended local hypodermic injections of solutions of calcium hypochlorite of a strength of 1 in 60 ; he gave 8 c.c. in and around the track of the fang. A solution made up in a

The Medicinal Use of Snake Venoms

Viperine Venoms in Hæmorrhages. The remarkable effect of Daboia venom in producing intravascular clotting led B. Burgess and R. G. Macfarlane to try 1 in 10,000 solutions on hæmophilic blood, in which it produced clotting within about twenty seconds. It also proved effective when applied on a plug of cotton wool after removal of teeth even in hæmophilic subjects. In America the venoms of the moccasin and the Fer de Lance vipers, and in Australia the tiger-snake venom have been tried with similar success and the same method has been used in epistaxis and by oral administration for hæmatemesis. J. Taylor found that Daboia venom can best be preserved as a 1 in 1,000 solution in equal parts of glycerine and water.

Cobra Venom as an Analgesic. Numerous cancer patients have been treated by D. I. Macht and others by 2 to 5 mouse-units of cobra venom by intramuscular injection daily or on alternate days with the relief of pain in many of them. Other painful conditions which have been reported to be relieved by this treatment include neuritis, neuralgia, sciatica, tic doloureux and angina pectoris not due to coronary thrombosis. Cobra venom acts slowly and is cumulative, but does not produce a drug habit. As snake venoms are very far from being sterile they should either be passed through an asbestos filter or 0·5 per cent. carbolic acid should be added before use by injection.

SCORPION STINGS

Scorpions have two poison glands connected with their spined tails, through which their venom is ejected. A maximum of 5 mg. of faintly acid thick fluid is injected by the common Indian form, *Buthus tumulus*, of which 0·5 mg. is fatal to a rabbit. It resembles the neurotoxin of colubrine snakes, but is far less powerful so that fatalities are chiefly met with in children. The stings are very painful and may cause a considerable degree of shock. In India scorpions are most commonly met with in the hills, where they are commonly found in houses.

The symptoms produced by scorpion stings include nausea, vomiting, profuse perspiration, rise of temperature and muscular cramps. The nervous symptoms include paralysis of muscles and stiffness of the neck and in serious cases respiratory failure and coma may ensue. Locally there are intense pain, redness and swelling.

Treatment. Antivenenes have been prepared against scorpion venoms in Algeria, Brazil, Mexico and other affected countries. They are effective in treatment especially when made from venoms of local species of scorpions. A dose of 20 c.c. should be given at once to patients of any age and repeated after an hour if there is no improvement. Careful watch on the patients should be kept for several hours.

In the absence of a specific serum a ligature should be applied

to hand must be used. The ligature should be applied to the upper arm or the thigh, for no degree of tightening of the ligature will stop the circulation in the forearm or leg, because of the presence of two bones in these parts. It is, however, useful also to apply another ligature just above the site of the bite. When the ligatures have been properly applied, steps can be taken to identify the snake and decide on the next line of action. The ligatures must not be left on too long, and they will be of little use if many minutes have elapsed since the introduction of the poison. They should be released for a few seconds every ten minutes to avoid ill-effects. C. H. Kellaway advises the application of a second ligature distal to the wound, together with an incision into a vein draining the region of the bite; when the upper ligature is released the site of the bite is thus flushed out with the venous blood, taking venom with it. Every outfit for the treatment of snake-bite should contain a piece of stout rubber cord suitable for use as a ligature.

The application of a ligature will delay considerably the absorption of the venom, especially in the case of viperine snakes which produce local clotting of the blood and extensive œdema, but if ten lethal doses of a colubrine venom have been injected by such a snake as a cobra a fatal dose may be absorbed by a dog within a few minutes, as shown long ago by Fayrer; with smaller doses a ligature will be of greater value, and will allow of longer time for other treatment to be applied. Local cauterisation of the site of a snake-bite, other than with permanganates or gold chloride, is of little value. If a bite has been received on a finger or toe from such a deadly and rapidly acting snake as a cobra or common krait, ligature and immediate amputation of the part is the most effective treatment. **Artificial respiration** is of value in colubrine poisoning if complete respiratory paralysis has not yet supervened. R. Linton has recorded a case of a patient almost moribund from colubrine poisoning, in which the use of one of Lord Nuffield's "iron lungs" revived the respirations, with ultimate recovery.

Some of the venom may be removed by immediate incision at the site of the wound to a depth up to half an inch, followed by suction which may be by the mouth if no apparatus is available. The venom, in small quantities is not dangerous when taken into the mouth.

A safety-razor blade is a useful addition for incising the site of the bite.

In **viperine poisoning,** L. Rogers showed that marked vasomotor paralysis produced by rattlesnake venom can be counteracted completely for some time by subcutaneous injections of adrenaline, and pituitrin is also of great value in maintaining the blood pressure (Fig. 79). For hæmorrhages large doses of calcium chloride or calcium lactate intravenously are indicated.

CHAPTER XXIII

DIETETIC ERRORS IN THE TROPICS

The diets of tropical countries are so varied that it is impossible to deal with them except in general terms. The following remarks refer chiefly to the diets of the densely populated tropical areas of Asia.

Statistics of the incidence of dietetic diseases give no real indication of the morbidity caused by faulty diets; for every case of illness that is reported as being due to a dietetic disease there are hundreds of people whose health is seriously impaired by malnutrition. Millions die every year because their resistance to infection has been undermined by diets that are inadequate or otherwise faulty.

In the case of every patient who is admitted to hospital in the tropics the question must be asked—to what extent is his illness caused or aggravated by faults in the diet?

Faulty diets will be dealt with very briefly under two heads—(1) dietetic errors of Europeans and (2) dietetic errors of indigenous communities.

Dietetic Errors of Europeans

Europeans in the tropics often fail to adapt their diet to the climatic conditions. The appetite is jaded in hot weather and so there is a tendency to eat small meals consisting mostly of animal food. This is often of poor quality, and it is made worse by bad cooking and by being kept hot for indefinite periods owing to irregular meal times. The food is therefore of low nutritional value and has a low vitamin content; the residue after digestion has not enough bulk to promote peristalsis and is more toxic than the residue from a vegetable diet.

The relatively high incidence of appendicitis and sprue among Europeans is probably associated with this kind of diet.

One course of flesh or fish twice daily is quite enough, but it should be of good quality and freshly cooked. The bulk of the diet ought to consist of wholemeal bread, vegetables, fruit, milk and butter. Plenty of water should be drunk, preferably between meals, and first thing in the morning.

Alcohol

A most serious dietetic error is over-indulgence in alcohol, which is responsible for much disability and shortening of life among Europeans in the tropics.

There is no evidence that alcohol, when taken well diluted with meals and in a strictly limited quantity, does any harm, but most of those who look on themselves as moderate drinkers are really drinking to excess. The chief danger of alcohol is its tendency to give rise to addiction. The advocates of total abstinence argue with reason that

when possible above the site of the sting, an incision made and a strong solution of permanganate of potash applied, together with ammonia. An injection of cocaine will help to relieve the pain. Secondary bacterial infections may result for which penicillin is indicated.

Prophylaxis. In Mexico gammexane has been found to be lethal to scorpions. A powder containing 5 per cent. D.D.T. is also lethal after a few days, so it should be dusted between the nocturnal haunts of scorpions and bedrooms and beds. Shoes should be inspected in affected areas before being put on.

POISONOUS SPIDERS

The most dangerous of the *Arachnida* are the "black widow" spider, or *Latrodectus mactans* of America and others of the same genus, such as the "red-backed" spider of Australia and New Zealand. They form webs in earth closets used in country districts. Hence the site of their bites is usually on the genitals or neighbouring parts. Care should therefore be taken to inspect earth closets before use.

These venoms have a neurotoxic action ; in addition some contain a hæmolysin. A bite may be fatal to guinea-pigs ; in man it produces muscular cramps, sickness, sweating and collapse with low blood pressure and in some cases pulmonary œdema, cyanosis and coma may ensue. Locally pain is intense either at once or an hour or so after the bite ; in the latter case the diagnosis is more difficult. Congestion, œdema or gangrene may result. Priapism, anuria and hæmaturia have been recorded. Secondary bacterial infections may cause fever.

Prophylaxis. Ten per cent. gammexane powder is fatal to the spiders and may be used for dusting earth closets to protect against poisonous spiders.

Treatment. This is on similar lines to that of scorpion poisoning described above. Local applications of ammonia, ichthyol and iodine are recommended for relief of pain. Saline 0·9 per cent. and 5 per cent. glucose solutions intravenously may be required to combat shock ; œdema of the lungs demands prompt venesection. Injections of adrenaline and of pituitary extract are of value in combating low blood pressure. An antivenene made by injecting sheep with the venom is of value.

Poisonous Lizards (*Heloderma*) occur in the deserts of Mexico. They have poison glands connected with recurved grooved teeth in the lower jaw, but their bites are rarely fatal to man. Treatment is similar to that for snake bites by local methods.

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ill effects likely to result from the sudden withdrawal of their customary drug. Small doses of alcohol given with meals may be useful for the debility of old age ; in this case there is little risk of habit-formation. Some medical men believe firmly in the value of alcohol in diseases like pneumonia and typhoid fever, while others consider it useless or even harmful ; in any case, it should always be withdrawn as soon as the acute illness is over, otherwise there is a grave danger of the formation of a habit which may have disastrous consequences in after life.

Indigenous races of tropical countries should be discouraged from the use of alcohol in any circumstances , they are notoriously liable to become addicts to the drug.

Dietetic Errors of Indigenous Peoples

Apart from actual shortage of food the chief fault in the diets of the people of tropical countries is the deficient supply of high-grade proteins and vitamins. The diets are often so bulky that there is incomplete absorption of the proteins contained in them. D. McCay found that when 19 oz. of rice were eaten daily 8½ grammes of protein were absorbed, but when the amount of rice was increased to 30 oz. only 6½ grammes were absorbed.

He found that certain sources of protein were unsatisfactory ; from a diet of millets, dal, and vegetables, containing 16 grammes of protein, only 9½ grammes were absorbed, while from a diet of wheat containing the same amount of protein 13 grammes were absorbed.

The strength and physical development of different races in India were closely associated with the amount of protein absorbed from the diet ; Europeans and Sikhs who absorbed over 0·25 gramme per kilogramme of body-weight were far more robust than Bengalis who absorbed only 0·11 gramme per kilo.

The low protein absorption of Bengalis was associated with a greater prevalence of kidney disease which was regarded as being the result of malnutrition of the kidney cells.

The more recent work of R. McCarrison further emphasises the importance of good diets : experimental rats fed on a " Sikh diet " were very healthy, while rats fed on a diet resembling that in use among the people of Southern India suffered from adenoids, otitis media, goitre, colitis, gastric ulcer and various other ailments.

The average daily diet of rice eaters in India is stated by Aykroyd (1940) to be : rice, 20 oz.; pulses, 1 oz.; leafy vegetables, ½ oz.; non-leafy vegetables, 4 oz.; vegetable fats and oils, ⅓ oz.; fish, meat or eggs, ½ oz. ; milk, negligible. In many parts of India even this scale of diet is seldom available ; it is deficient in animal proteins, fats, calcium and vitamins.

The part played by vitamin deficiencies is dealt with in the next chapter.

nobody knows to begin with that he is not one of the people who will acquire the alcoholic habit.

The "treating" custom is responsible for most of the excessive consumption of alcohol; left to themselves, most people would be content with one or two mildly alcoholic drinks daily and little harm would be done. After a succession of rounds of pegs the insidious effects of the drug are experienced; diffidence and self-consciousness vanish and are replaced by a feeling of confidence and release from restraint. Victims of the "inferiority complex" are specially likely to be attracted by the temporary sensation of competence that is produced by alcohol, the depression that follows is unpleasant but can be cured by a further dose, and so there is a fatal tendency to take gradually increasing quantities.

Anyone who feels that he must have a few daily pegs to keep himself going is already on the way to becoming an addict, though it may be years before the damage done by alcohol becomes apparent.

It has been clearly proved that alcohol is not necessary to health in the tropics; in small quantities such as two small pegs a day with meals it is a very minor vice against which the only objection that can be raised is that so many people cannot keep within safe limits.

The cocktail habit is specially pernicious; concentrated alcohol taken on an empty stomach does far more harm than well-diluted pegs with meals.

Light wines taken in moderation with meals are not open to serious objection, but beer, for some reason, is not well tolerated by most people in hot weather in spite of its low alcoholic content.

Far more harm is done by constant tippling than by getting drunk at infrequent intervals and abstaining for the rest of the time; indeed many people suffer from very serious ill effects who have never been obviously intoxicated.

The effects of alcohol are dealt with in a scientific and impartial manner in a book published by the Medical Research Council, "Alcohol: its Action on the Human Organism"; this should be read by those who wish to get reliable information on the subject.

In that book it is shown that alcohol is *not* a stimulant, but a narcotic, and that it gives rise to a feeling of competence which is quite unjustified and is responsible for many motor accidents.

The devitalising effects of alcohol are well shown by an analysis of the fatal results in 3,422 cases of pneumonia in a large hospital in Chicago. The death rate was 50 per cent. in heavy drinkers, 34·4 per cent. in moderate drinkers, and 22·5 per cent. in abstainers.

In the tropics alcohol predisposes to certain diseases such as liver abscess, pneumonia, heat stroke and tropical neurasthenia. Alcoholics are notoriously bad subjects for anæsthetics and surgical operations.

When addicts meet with an accident or fall sick it may be necessary to allow them a ration of alcohol to prevent delirium tremens or other

on the milk supply of hospitals, not only to ensure its purity on arrival, but also to prevent pilfering by attendants.

A ration of orange juice or other anti-scorbutic must be provided for every patient who is kept on an invalid diet.

The prejudices of the patients often have to be overcome, some of them object to milk because of the traditional belief that it is converted into phlegm and so is unsuitable for persons who have a cough. Milk is also accused of causing diarrhœa: the foundation of this prejudice is that milk is often regarded as a drink and is taken in addition to a [illegible]lic[illegible]he digestive organs are overtaxed. Milk suffers from [illegible]g[illegible]ng time, it should be pasteurised or brought quickly [illegible] and then cooled at once.

J. W. D. MEGAW

The inadequate and otherwise faulty diets of tropical countries constitute a difficult and complex problem. When girls become mothers at the average age of about sixteen, irrespective of whether any provision has been made for the support of a family, the population tends to increase out of all proportion to the available food supply and it becomes necessary to grow crops which yield the greatest possible bulk on each acre of cultivated land, so that protective foods like milk which require a far larger acreage for each person cannot be produced.

In India the population increased by 50 millions in the ten-year period, 1931 to 1941, so that any improvement in the nutritive properties of the diet must have been out of the question.

Similar conditions already exist, or are coming into existence, in most of the tropical countries; the problem directly concerns the medical profession, whose efforts to control preventible diseases must inevitably fail unless radical improvements are effected in the economic conditions of life. Improved methods of agriculture and social reforms are the only possible remedies; medical men should seize every opportunity of pointing out the necessity for the introduction of these.

Drug Addiction. Opium, hemp preparations, cocaine, and other drugs, are factors in causing disease in the tropics, but the mischief done by them is probably much less than that caused by alcohol in European countries.

Betel Chewing. This often amounts to a real vice; stomatitis, pyorrhœa alveolaris and gastritis are often caused by excessive betel chewing.

The plug of betel is sometimes kept for a considerable time between the gum and the cheek, where it sets up a chronic inflammation of the mucous membrane: many cases of cancer of the cheek and gums are associated with the persistent irritation caused in this way. The chief constituents of betel are betel leaf, areca nut, tobacco, unslaked lime and condiments. There is no definite knowledge as to which of these ingredients is the essential factor in causing cancer; probably lime plays the chief part as it is intensely irritating.

Cancer of the stomach seems to be rare in many parts of India, and also in most of the other tropical countries. The probable cause of this peculiarity in the distribution of cancer is that the people of tropical countries do not drink scalding-hot liquids and so escape from the constant irritation to which many people in cold countries subject their stomachs.

In some parts of South India cancer of the stomach and peptic ulcers are common: in these places the people eat very hot curries which may well contain carcinogenic substances.

Defects of Hospital Diets. Nutritious diet forms an essential part in the treatment of patients in the tropics, especially as many of them are already suffering from malnutrition. A strict watch must be kept

on the milk supply of hospitals, not only to ensure its purity on arrival, but also to prevent pilfering by attendants.

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CHAPTER XXIV

DIETETIC DISEASES IN THE TROPICS

DISEASES caused by faulty diets are sometimes called "nutritional diseases," but this name is not suitable because there are many causes of nutritional disorders besides faults in the diet.

The chief dietetic diseases are shown in the following table in which they are classified according to the generally accepted views of their causes. But, as will be seen later, the ætiology of the clinical conditions commonly called vitamin-deficiency diseases is by no means so clear and simple as the table suggests.

There are other complications in connection with the dietetic diseases, among these are the following: (1) in many cases two or more faults in the diet occur simultaneously, when this happens treatment directed against one of the causes will be unsatisfactory; (2) cases of dietetic disease are often encountered in which the cause

CLASSIFICATION OF THE CHIEF DIETETIC DISEASES OF TROPICAL COUNTRIES

(Showing the generally accepted views of their causes)

Type of Disease	Name of the Disease	Cause
Diseases due to dietetic excess.	Dietetic obesity and dietetic diabetes.	Excessive use of carbohydrates and lack of exercise.
Starvation diseases .	Dietetic malnutrition and famine œdema.	Insufficiency of calories, proteins, etc.
Vitamin-deficiency diseases.	Rickets and osteomalacia.	Deficiency of vitamin D.
	Xerophthalmia and night-blindness.	Deficiency of vitamin A.
	Scurvy.	*Deficiency of vitamin C.*
	Ariboflavinosis.	Deficiency of riboflavin.
	Beri-beri.	Deficiency of vitamin B_1.
	Pellagra.	*Deficiency of nicotinic acid.*
Dietetic intoxications .	Lathyrism.	Poisoning by seeds of *Vicia sativa.*
	Epidemic dropsy.	Poisoning by oil of *Argemone mexicana.*

has not yet been discovered so that the only available diagnosis must be "dietetic disease of unknown ætiology"; (3) a dietetic disease often occurs in a patient suffering from some other disease in which malnutrition is caused by disturbances of digestion, assimilation, or metabolism; so that often it is impossible to decide whether a dietetic fault or a coexisting disease is the chief cause of the illness.

These difficulties can usually be overcome by observing simple rules which will be stated later in this chapter

Dietetic Obesity and Dietetic Diabetes

These diseases are exceedingly prevalent in tropical countries among persons who eat large quantities of carbohydrate foods and lead sedentary lives. The first effect of these habits is obesity; in due course this is followed by glycosuria and then by pronounced diabetes. These conditions are often attributed to heredity, but this cannot be regarded as the cause, seeing that other members of the same families who are compelled to do physical work and lead frugal lives are no more prone to the diseases than the rest of the community. The obvious explanation seems to be that a great strain is imposed on the cells of the liver and pancreas that are responsible for carbohydrate metabolism. These cells are first hypertrophied by their efforts to cope with the extra work imposed on them, and then become atrophied as a natural consequence of over-activity.

Climate plays a part, because in hot weather a smaller amount of the carbohydrates is used up in the maintenance of body-heat.

Professional men with comfortable incomes are the chief victims of the syndrome, many of them have diabetes before reaching middle age.

The prevention and treatment are on obvious lines; when diabetes has developed the islet cells of the pancreas are usually so severely damaged that the patients must resign themselves to insulin treatment and restricted diet for the rest of their lives.

Dietetic Malnutrition

This is so common in many parts of the tropics that it has come to be regarded as the normal condition of the inhabitants. In reality it is the *most important of all the tropical diseases; it causes life-long* disablement in hundreds of millions of people; indirectly it is responsible for millions of deaths every year. The cause is an insufficient supply of proteins, calories, fats, vitamins, and other substances, needed to maintain growth and health.

The severest form of dietetic malnutrition is called Famine Œdema or Famine Dropsy; this is likely to occur when the proteins in the diet fall below 30 grammes daily and the calories are less than 1,000. It is described briefly on p. 484.

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	Xerophthalmia and night-blindness.	Deficiency of vitamin A.
	Scurvy.	Deficiency of vitamin C.
	Ariboflavinosis.	Deficiency of riboflavin.
	Beri-beri.	*Deficiency of vitamin B_1.*
	Pellagra.	Deficiency of nicotinic acid.
Dietetic intoxications.	Lathyrism.	Poisoning by seeds of *Vicia sativa.*
	Epidemic dropsy.	Poisoning by oil of *Argemone mexicana.*

PROPERTIES, DOSAGE, ETC., OF THE CHIEF VITAMINS

Names of the Vitamins	Chief Diseases Cured or Benefited by the Vitamin	Adult Therapeutic Daily Doses of the Vitamin in (a) International Units	(b) Milligrammes	Daily Needs in Milligrammes or Units
Vitamin A (carotene is the precursor)	Xerophthalmia and night-blindness.	6,000 to 30,000	6 to 30	5 mg.
Vitamin B_1 (thiamin or aneurin)	*Beri-beri, alcoholic neuritis, etc.*	2,000 to 10,000	6 to 30	2 mg.
Vitamin B_2 complex. (a) riboflavin	Ariboflavinosis.	No unit has been laid down.	1 to 3	2 mg.
Vitamin B_2 complex. (b) nicotinic acid or the "P.P." factor.	Pellagra, sprue, etc.	Do. Do.	50 to 500	20 mg.
Vitamin C (ascorbic acid)	Scurvy.	2,000 to 5,000	100 to 250	70 mg.
Vitamin D (calciferol)	Rickets.	2,000 to 3,000	0·05 to 0·075	300 units[1]
Vitamin E (tocopherol)	Some forms of abortion and sterility.	No unit has been laid down.	9	3 mg.

[1] Infants and children need as much vitamin D as adults; pregnant women need 50 per cent. more during the second half of pregnancy.

Vitamin Deficiencies

Little was known about vitamins till the early years of this century though for a long time it was common knowledge that sailors and others who lived for long periods on stale foods suffered greatly from scurvy, and also that this disease could be prevented and cured by fresh fruit and vegetables.

Sir Frederick Hopkins (1906–12) found that animals fed on purified mixtures of all the substances then regarded as essential to nutrition quickly lost weight and soon died. By the addition of small amounts of milk the animals were restored to good health.

The presence of " accessory food-factors " in natural diets was thus demonstrated, and it was assumed that these factors were nutritious substances which, though needed in very small quantities, were essential to health.

In 1912 Funk called these substances " vitamines " (amines of life), but when they were found to be different from amines the letter " e " was dropped and they came to be called vitamins.

In 1915 McCollum found that there were two types of these accessory factors to one of which the name " fat-soluble A " was given while the other was called " water-soluble B." Each of these factors was later found to be of a complex nature, and as research progressed other letters of the alphabet were used to designate the vitamins. Vitamin B was soon found to include two vitamins which were called B_1 and B_2 ; and later B_2 was shown to comprise at least six distinct vitamins.

Most of the vitamins have now been isolated in pure form and their chemical compositions have been determined so that it is possible to give them suitable names, to estimate the amounts of each contained in foodstuffs, and to state their doses in terms of weights.

For many years speculation has ranged over various possibilities concerning the mode of action of vitamins. At one time the toxin neutralisation hypothesis dominated the field.

Eijkmann, in 1897, was the first to suggest the occurrence of poisons in natural foodstuffs ; he found that fowls fed solely on polished rice developed neuritis which could be cured by rice polishings ; his view was that the inner part of the rice grains contained a toxin, and that the outer layers contained an antidote.

E. Mellanby, in 1926, suggested that vitamin D acted partly by neutralising a toxic substance associated with a diet of cereals, especially oatmeal.

Beck (1941) produced symptoms of deficiency of vitamin A in rats fed on over-cooked fats even when the animals were given other food well supplied with the vitamin. These fats must have contained substances which neutralised vitamin A and so, directly or indirectly, acted as poisons.

György (1941) found that a diet consisting largely of raw white of egg caused a scaly dermatitis in rats ; a vitamin of the B_2 group called biotin cured the dermatitis which must have been caused by a toxin because it was not produced when the egg-white was thoroughly cooked though the diet otherwise remained the same.

Willison (1943) has proved that vitamin C can neutralise the diphtheria toxin *in vitro*. This had already been stated by Harda (1934) and others, but their findings were disputed. Vitamin C is also said to neutralise the tetanus toxin.

Other recent investigations showing that the widely accepted views of the part played by vitamins need drastic revision are those of Sure (1939), who found that rats could maintain good health on a diet devoid of vitamin C provided that an adequate amount of vitamin B_1 was supplied. Dogs on a diet containing no vitamin B_1 developed ulcers of the mouth which could be cured by vitamin C even though vitamin B_1 was entirely absent from the diet.

Najjar and Holt (1943) kept nine human beings in good health on a special diet of casein, vegetable fats, sugar, mineral salts, and all the vitamins in normal quantities, with the exception of vitamin B_1, which was present in very small quantities, of 0·2 milligrammes. After a long period on this diet vitamin B_1 was entirely withheld, yet for a further period of five weeks four of the persons remained in good health and continued to excrete the vitamin in their stools.

Although far from complete, much information has been obtained in recent years about the actual roles played by vitamin factors. It is clear that most of them are essential components of the complicated enzyme systems which are responsible for intracellular respiration and metabolism. For the intracellular oxidation of glucose, enzymes associated with the vitamin-B complex are necessary. Cozymase, a component of the intracellular enzyme system requires nicotinic acid for its formation. With deficiency of vitamin B_1 pyruvic acid accumulates in the body cells and cannot be oxidised.

This upset of the normal intracellular enzyme chain mechanism explains the similarity of nervous symptoms caused by alcoholic neuritis and beri-beri as both are ultimately due to non-availability of thiamin. At one time it was suggested that both were due to the positive action of toxins.

Further, there is a quantitative relationship between the relative amounts of carbohydrate and of vitamin-B complex which must be absorbed if normal metabolism is to take place. The amount of vitamin B which would suffice for a person living on a well balanced dietary of protein, fat and carbohydrate would be quite inadequate for one of the same weight living almost exclusively on a carbohydrate diet such as rice.

Recent work indicates the important role played by the intestinal flora which may (1) synthesise certain essential food factors, *e.g.*, folic

	Fat Soluble			Water Soluble		
	Vitamin A	Vitamin D	Vitamin E	Vitamin B_1	Vitamin B_2 complex	Vitamin C
Chemical name	Carotene is the precursor.	Calciferol.	Tocopherol.	Aneurin or Thiamin.	Riboflavin, Nicotinic acid, Adermin, etc.	Ascorbic acid or Cevitamic acid.
Chief properties	Growth promoting, anti-xerophthalmic.	Anti-rachitic, promotes the utilisation of calcium and phosphorus.	Anti- sterility.	Anti-neuritic, growth promoting.	Anti-dermatitis, Anti-pellagra, Anti-anæmia, etc.	Anti-scorbutic.
Vitamin Content of Certain Foods	Units per gramme	Units per gramme		Units per gramme		Units per gramme
Cod-liver oil	600–3,000	50–300	0	0	0	0
Spinach and other thin green leaves.	40–100	0	++ to +++	0·3–1·8	+ to ++	2–12
Egg	40–80	2–5	+++	1·4	++	Trace.
Butter	20–50	1–4	+++	0	0	Trace.
Fresh milk	3–10	0·1–1	+	0·2	+ to ++	Trace.
Wheat embryo	+++	0	+++	8·5–18·7	++	0 or trace.
Whole wheat	1·0	0	+	2·3–3·4	± to +	0 or trace.
Rice (parboiled)	± to +	0	?	1·0	+	0 or trace.
Rice (polished)	0	0	0	0·3	Trace.	0 or trace.
Red gram (Arhar Dal).	2·2	0	?	1·0	+	0 or trace.
Yeast	0	0	0	6–23	++ to +++	0
Lemon juice	+	0	0	+	0	12
Orange juice	+	0	+	+	Trace.	10
Tomatoes (ripe)	3·2	0	0	0·4	+	4–6

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acid (in the rat 70 per cent. of the folic acid required may be synthesised by intestinal bacteria) ; or (2) compete for and utilise certain essential factors in the intestinal contents and so prevent their absorption for use by the tissues. The ability of certain bacteria to compete for and seize available growth factors is now well recognised. It is thought that a grossly abnormal bacterial flora in the intestine may thus diminish the availability for absorption of essential food factors taken by mouth. Achlorhydria or hypochlorhydria of the stomach contents plays an important part in determining abnormal *p*H values of the intestinal contents, thus providing an abnormal medium for unusual flora.

Much fundamental information of importance in connection with nutrition has been obtained from work carried out on the mechanism by which sulphonamides inhibit the multiplication of certain micro-organisms. They do so by competing for and taking up the *p*-amino benzoic acid (*p*.a.b.a.) which is essential for the growth of certain bacteria. If *p*.a.b.a. is added in excess sulphonamide action is annulled. The prolonged use of sulphonamides by mouth may seriously interfere with the growth of certain bacteria which may help to produce essential food factors and may thereby possibly induce nutritional deficiencies. There is reason to believe that the prolonged oral use of certain antibiotics such as aureomycin may interfere with beneficial synthesis by intestinal bacteria.

The action of phytic acid as a competitor for calcium is now well established ; amounts of vitamin D adequate for the proper absorption of calcium from an average diet may be inadequate if the food taken contains much phytate—as it does in diets rich in oatmeal and brown bread. A high proportion of the calcium ingested enters into combination as calcium phytate and is not available for the maintenance of the ionic balance of the body tissues and fluids and for bone building.

Less stress is now laid on the positive action of toxic materials in the food in causing deficiency diseases but the condition of cicerism in rats (ataxia, coma and convulsions on feeding with the chick pea containing the protein cicerin) clearly indicates the possibilities of analogous happenings in human dietaries. Cicerism can be masked or prevented by adding small quantities of choline or methionine to the toxic diet, but if the reinforced toxic diet is over-cooked so that the choline is damaged or destroyed cicerism occurs promptly.

Some other points connected with vitamins are : (1) Inadequate supplies of vitamins are believed to cause a great variety of disabilities which are not so characteristic in type as to enable the physician to diagnose a deficiency disease. Debility, diarrhœa, anæmia, and lowered resistance to infection, may often be due to a shortage of vitamins not amounting to frank deficiency. (2) Even when the symptoms point to special deficiency of one vitamin there is often a multiple deficiency, and in many cases there are other faults in the diet such as deficiency

of animal proteins, iron, calcium, etc. For this reason treatment by pure vitamin preparations often gives less satisfactory results than treatment by natural foods rich in the vitamins. (3) Excessive doses of vitamins may be harmful; for example, vitamin D in very large quantities causes a deposition of calcium in the arteries, over-dosage with vitamin B_1 causes nervousness and insomnia, and nicotinic acid may cause flushing and other unpleasant symptoms. These effects are not produced when the vitamins are supplied in natural foods. (4) The vitamin content of some foods is very variable; some samples of cod-liver oil contain six times as much vitamin D as others, and butter or milk may vary greatly in their vitamin content according to the health and diet of the cows. (5) Different experimental animals show great variations in their responses to diets deficient in the same vitamins; birds deprived of vitamin C get polyneuritis rather than scurvy; a diet of white bread causes scurvy or polyneuritis or both these diseases in man, whereas in guinea-pigs it causes only scurvy. Clearly the final test of a diet must be its effects on human beings although animal experiments yield much valuable information. (6) In some diseases the vitamins contained in the food are destroyed in the alimentary canal. (7) Food stored in unfavourable conditions may lose much of its original vitamin content; so also food that has been over-cooked or kept hot for a considerable time after cooking loses a large percentage of its vitamins, especially vitamins C and B_1. The water used in cooking dissolves these vitamins, so that if it is thrown away there is a great wastage. (8) There are wide differences of opinion with regard to the quantities of each vitamin that are needed to maintain health; for example, the estimated requirement of vitamin A as stated by different experts varies from 1,000 to 10,000 units. Apart from the factors already mentioned, it seems likely that much depends on the kind of food that is eaten; with certain foods there is a greater need for vitamins than with others. Many persons maintain good health on far smaller quantities of certain vitamins than those stated in the table. These quantities must be regarded as ideals to be aimed at and as being ample in any conditions that are likely to occur rather than as being always essential for the needs of the body. (9) A good supply of all the vitamins is needed but nothing is gained by giving excessive amounts; there have been cases in which very large doses of one vitamin in the pure state have caused toxic symptoms, or even have caused symptoms of the kind that result from deficiency of another vitamin.

The whole subject of the vitamin-deficiency diseases is so complicated that the student is likely to feel bewildered; he will often be at a loss to decide which vitamins are deficient in a particular case and which name should be given to the disease but he need not feel unduly depressed by these difficulties; he can be assured of being able to deal effectively with every case of dietetic-deficiency disease if he observes

the following simple rules : (1) he should investigate the diet on which the patient has been living and then prescribe a diet well supplied with every vitamin and with all the ingredients of an ideal diet ; (2) he should give, in addition, therapeutic doses of any special vitamin whose deficiency is suggested by the symptoms ; (3) he should withhold any article of diet that is specially associated with the type of disease from which the patient is suffering, for example rice in beri-beri, and maize in pellagra ; and (4) he should treat any other disease from which the patient may be suffering, such as malaria, dysentery, helminthic infection, etc.

If these rules are observed there will rarely be any difficulty in the prevention and treatment of diseases associated with dietetic deficiency, dietetic intoxication, or a combination of these two factors.

In the following pages certain diseases are classed as being "associated with vitamin-deficiencies," but this does not imply that the basic cause of these diseases is solely a deficiency of the diet in respect of the vitamins concerned.

DISEASES ASSOCIATED WITH DEFICIENCY OF CERTAIN VITAMINS

I. Deficiency of Vitamin D

Rickets and osteomalacia are associated with deficiency of vitamin D in the diet ; many cases of vague ill health are likely to be due to a shortage of this vitamin.

Toxic factors in the diet cannot be excluded and it would, perhaps, be more accurate to describe the diseases as being "curable by vitamin D."

Rickets. Rickets can be caused by deficiency of vitamin D in the diet ; it can be prevented and cured by a diet rich in the vitamin. Reliable brands of cod-liver oil, halibut-liver oil, fresh butter, fresh milk and eggs are rich sources of vitamin D. No vegetable contains any appreciable quantity of the substance. The vitamin has been prepared in pure crystalline form by irradiation of ergosterol : the crystals are called "calciferol." Sunlight plays an important part in preventing and curing rickets. The action of the ultra-violet rays of the sun on the skin produces vitamin D from the circulating blood, but the body must contain the precursors of the vitamin, otherwise exposure to sunlight will be useless. These precursors are derived from the diet, so that if the food is grossly deficient in them sunlight fails to prevent or cure rickets.

Vitamin D promotes the utilisation of calcium and phosphorus by the body. Both of these elements must be present in the diet in sufficient quantities.

Most of the diets in common use contain enough calcium, phos-

phorus and vitamin D to prevent rickets provided that the body is sufficiently exposed to sunlight. Cases of severe rickets are not very common in India, because the mothers' milk is fairly well supplied with vitamin D, and infants are usually allowed to play in the open air. In some parts of South and West India rickets in a mild form is common among children who are reared in dark rooms. There is reason to believe that most of the children of all tropical countries suffer from a shortage of the vitamin, even though there may be no gross deficiency. One and a half pints of milk daily with two teaspoonfuls of a good quality of cod-liver oil will provide an ample ration of calcium, phosphorus and vitamin D for a growing child.

Ordinary window glass shuts out a large proportion of the ultra-violet rays so that a room may be well lighted and yet unsuitable for the prevention of rickets. Daylight in smoky towns is very deficient in ultra-violet rays, especially in winter. Many Europeans in the tropics suffer from deficiency of ultra-violet radiation because of an exaggerated fear of the tropical sun. In the the heat of the day, the sun should be avoided, but in the morning while the air is still cool, the sun's rays are health-giving and should be welcomed.

Minor degrees of malnutrition due to shortage of vitamin D and lack of light are much more common than frank rickets, hence the importance of ensuring a proper supply of both vitamin and daylight to infants and young children. The cure of rickets is best effected by cod-liver oil or other rich source of the vitamin and by exposure of the surface of the body to sunlight.

Osteomalacia. This is adult rickets ; it is very common in some towns and cities in India and Kashmir, also in other countries where the *purdah* custom prevails. Many cases have been reported from China.

The disease does not occur among people who lead an outdoor life except in a few places like the Kangra valley in the Punjab, where the diet is so grossly deficient in pro-vitamins that exposure to sunlight fails to prevent the disease.

The causes are exactly the same as those of rickets.

The disease rarely appears in young children, who are usually allowed to go out freely into the open air even in the case of families which observe the *purdah* custom. When the age of puberty approaches the young girls are kept indoors and so become liable to the disease. Pregnancy and lactation greatly increase the need for vitamin D so that young married women are specially affected ; middle-aged and even elderly women are sometimes attacked, but males very rarely show obvious symptoms of the disease.

The disease begins with weakness, pains in the pelvic region or " girdle " pain. Tetany and other forms of muscular spasm are common. In severe cases the bones, especially those of the pelvis, become softened and deformed so that parturition becomes difficult or even impossible owing to narrowing of the outlet.

The prevention and treatment are the same as for rickets, but the deformities when well established cannot be rectified.

II. Deficiency of Vitamin A

Deficiency of vitamin A is responsible for a great deal of ill-health in some tropical countries, especially among young children.

Xerophthalmia and night-blindness are the chief diseases caused by deficiency of the vitamin, but many cases of malnutrition and obscure illness are doubtless due to shortage not amounting to serious deficiency.

Lowered resistance to infection, anæmia, some kinds of stone in the bladder, and peptic ulcers, have been attributed to deficiency of this vitamin.

In most cases of vitamin-A deficiency there are other dietetic defects, so that the clinical picture is usually of a complicated type.

Xerophthalmia and Keratomalacia. This disease is associated with deficiency of vitamin A in the diet.

The first symptoms are drying up of the lachrymal secretion and a dry waxy appearance of the conjunctiva, called xerophthalmia.

In severe cases the condition becomes one of keratomalacia with keratitis, ulceration of the cornea, and finally in some cases complete destruction of the eye-ball.

In Southern India, according to R. Wright, the chief cause of blindness is keratomalacia.

Night Blindness. This often precedes or accompanies xerophthalmia. The traditional treatment by goat's liver, which is rich in vitamin A, has been completely justified by modern research.

Damage to the retina by glare is often a predisposing factor ; it may even be the sole cause of night-blindness.

Treatment of Vitamin-A Deficiency

Cod-liver oil of high potency, butter, eggs, fresh milk, and green leafy vegetables, are the chief remedies, but the diet must be well supplied with high-grade proteins and all the other vitamins.

Ghee is not a reliable source of vitamin A ; it is often adulterated, and even when pure much of the vitamin may be destroyed by prolonged heating in the course of its preparation.

III. Deficiency of Vitamin C

Scurvy. Scurvy is associated with deficiency of vitamin C (ascorbic acid). In its frank form this disease is not common in the tropics in spite of the fact that many persons live on diets poorly supplied with the vitamin.

Breast-fed infants rarely get scurvy though doubtless they often

suffer from malnutrition due to shortage of the vitamin in their mother's milk.

Severe scurvy, with spongy and bleeding gums, hæmorrhages under the periosteum, debility and anæmia, is seen chiefly in persons who live for long periods on dried grains and other stale foods grossly deficient in vitamin C.

Vitamin C has a strikingly curative action on scurvy, but attempts to produce scurvy in human beings by feeding them on diets deficient only in vitamin C have yielded puzzling results. So also have the animal experiments of Sure, who found that rats could thrive on diets devoid of vitamin C provided that plenty of vitamins of the B-complex were supplied.

These results, together with the known power of vitamin C to neutralise certain bacterial and other toxins *in vitro*, suggest that a toxic factor in the diet may play a part in causing scurvy.

The value of a plentiful supply of the vitamin in the diet is not confined to its power of preventing scurvy ; it is likely that millions of persons in the tropics are suffering from malnutrition which could be prevented and cured by a diet rich in vitamin C.

In the treatment of scurvy attention should not be restricted to the provision of the vitamin ; the diet ought to be well supplied with all the vitamins and other essentials of an ideal diet.

Among the richest natural sources of the vitamin are oranges, lemons, pomeloes, tomatoes and green vegetable leaves. Potatoes, though not very rich in the vitamin, are of great value because of their keeping properties and because of the large quantity that can be eaten ; most of the diets in the tropics would be greatly improved by the inclusion of potatoes.

Germinating grains are valuable in special conditions ; pulses can be soaked in water for twelve hours at 90° F. or for twenty-four hours at 60° F. ; then the water is drained off and the grain is kept in a vessel large enough to provide for great expansion of the contents. After a day or two, according to the temperature, the grain will sprout. It is eaten raw or lightly cooked within three or four days. Prolonged cooking destroys most of the vitamin in germinating grain, fruits and vegetables, but properly prepared orange or lemon juice remains rich in the vitamin for long periods.

Dried fruits and vegetables are poor in vitamin C.

IV. Deficiencies of Vitamins of the B-Group

The chief diseases associated with deficiencies of the vitamins of the B-group or complex are beri-beri, pellagra and ariboflavinosis.

Before studying these diseases the reader ought to refer to the discussion of the properties and mode of action of vitamins in general (see page 446).

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rice by microbic action which was promoted by storage in hot and damp conditions. The gastro-intestinal disturbances followed by polyneuritis were regarded as being analogous with those caused by arsenic and other poisons. This theory fell into the background after the discovery of the vitamin-B complex but it still has influential advocates.

Japanese observers have extracted a poison which they called "orizotoxin" from certain samples of rice. Acton, Chopra, Barrett, Stockman, and several others, have also reported the extraction of a poison from rice, but the exact composition of the toxic substance has not been determined.

The Toxi-Infection Theory. This has had many supporters; it differs from the intoxication theory in that the poison is believed to be generated by bacteria in the gastro-intestinal tract instead of being present in the rice before it is ingested. Our knowledge of the thiamin-producing and thiamin-destroying organisms of the intestinal canal is still elementary.

The Vitamin-B_1-Deficiency Theory. Deficiency of several food factors, especially proteins, had long been suspected of causing the disease, but shortly after the discovery of "water-soluble vitamin B," deficiency of this substance came to be generally accepted as the cause.

Stanton and Fraser (1909–11) found that when the disease was prevalent among labourers whose diet consisted largely of over-milled rice it could be controlled by changing the diet to one of under-milled rice which was much richer in the vitamin-B complex. Eijkman, in 1897, had already noticed the prevalence of the disease among prisoners who were living chiefly on over-milled rice; he had also found that fowls fed solely on this kind of rice developed polyneuritis within three or four weeks and that the fowls recovered when they were given extracts of rice-polishings in addition to the diet of over-milled rice. His view was that the inner part of the grain contained a poison and that the outer layers contained an antidote for this. He neither asserted nor denied that the disease in fowls was the same as human beri-beri.

When vitamin B_1 was isolated as a separate factor it came to be regarded as the substance whose deficiency in the diet caused the disease, but at present there is a tendency to regard deficiency of other vitamins as playing a part, and also to attach importance to other faults in the diet. But although vitamin-B_1 deficiency has been so widely accepted as the cause there have always been observers who found it difficult to accept this theory. The following objections have been raised :—

(1) The experimental neuritis caused in fowls and other animals by a diet deficient in vitamin-B complex differs from human beri-beri to a striking degree; the tissues of the animals become shrunken and the heart is atrophied in most cases.

(2) Attempts to produce beri-beri in human beings by feeding them

(I) BERI-BERI

Definition. Beri-beri is usually defined as a dietetic polyneuritis caused by deficiency in Vitamin B_1 (thiamin or aneurin).

It has not, however, been shown that the disease can be caused by diets whose only fault is deficiency of vitamin B_1 and, for reasons which will be stated below, it is not yet possible to give a definition based on conclusive evidence so that the following brief statement must take the place of a dogmatic definition. Beri-beri is a name given to certain types of dietetic polyneuritis which are described later and which occur almost exclusively among persons living chiefly on over-milled rice or other diets containing too little vitamin E and too large a proportion of carbohydrates ; the diets are always faulty in other important respects. Beri-beri usually occurs as outbreaks among persons living on the same kinds of diet.

It should be added that there are certain types of dietetic polyneuritis which are called beri-beri by some observers but are regarded by others as different diseases.

In view of the unsolved problems connected with the ætiology of the disease it is still considered desirable to mention the theories held by various groups of observers in the past as well as those that hold the field at the present time. One thing can be said with confidence, beri-beri never occurs among persons who live on wholesome and well-balanced diets so that it is possible to lay down dogmatic rules for the prevention and control of outbreaks.

History. Beri-beri appears to have been known to the Chinese many centuries ago. The first Western physicians to recognise the disease were the Dutch, who encountered it in their early voyages to the Far East.

In the early years of the nineteenth century, Marshall described two conditions, one of which was a paralytic disease to which he gave the name " barbers," the other was a dropsical disease which he called " beri-beri."

In 1835 Malcolmson in India, pointed out, that both the dropsical and paralytic manifestations often occurred in the same person, and that they might appear simultaneously or might succeed one another in the same patient, so that since his time the " wet " and " dry " forms of beri-beri have been generally recognised.

The German physicians Baelz and Scheube, working in Japan, showed that the neuritis of beri-beri was of the same type as alcoholic and diphtheritic neuritis.

Ætiology. There has always been a good deal of controversy about the exact cause of the disease. Among the many theories the following are the most important :—

The Intoxication Theory. The chief advocate of this was Braddon, who held that the cause was a poison generated in over-milled (polished)

vitamin-B complex. Barratt also found that extract of the offending rice was toxic to animals.

(5) The special association of the disease with rice and its rarity among persons living on other diets poor in vitamin-B complex suggests a toxin rather than a deficiency as the cause.

In apparent contradiction to these objections are the curative action of vitamin B_1 and the special prevalence of the disease among groups of persons whose diets are deficient in that vitamin.

The Combined Intoxication and Vitamin-Deficiency Theory. The generally accepted modern view of the ætiology of beri-beri is that the disease is caused by a combination of intoxication and vitamin deficiency. The actual cause is believed to be a poison (pyruvic acid) which is normally produced during the metabolism of carbohydrates and accumulates to a harmful degree when, and only when, the natural antidote (carboxylase) derived from vitamin B_1 is not being produced in sufficient quantity to neutralise the poison.

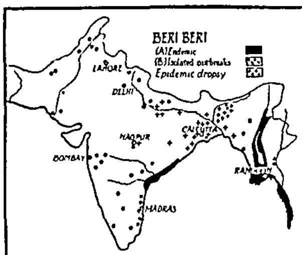


Fig. 80. Map of distribution of beri-beri in India.

This explanation of the causation of beri-beri is not accepted by all the workers on the vitamins, but deficiency of vitamin B_1 and an undue proportion of carbohydrates are undoubtedly the most obvious faults of the diets eaten by communities affected by beri-beri. There must, however, be other faults because it has not been possible to produce the disease in human beings by feeding them on diets that are faulty only in these two respects. Such faults as other vitamin deficiencies and the possible presence of toxic substances, contained in the food, analogous to cicerin (see p. 450), or produced in the food during improper shortage, cannot be ignored.

Geographical Distribution. The disease is rare except in places where rice enters into the dietary to a considerable extent ; accordingly it is specially prevalent in the tropical and sub-tropical countries of the Eastern Hemisphere, where rice is the staple article of diet. The chief centres of the disease are—Japan, China, Indo-China, Siam, Malaya, the Dutch East Indies, Ceylon, Burma, and Southern India.

Between 1920 and 1929 the average yearly number of deaths from beri-beri in Japan was 17,000. Large towns are much more heavily affected than rural areas and small towns.

on diets deficient only in vitamin-B complex have not been successful. The carefully conducted experiments of Strong and Crowell showed that nutritional disorders "suggestive of beri-beri" occurred in ten of seventeen persons who had lived for more than two months on a diet consisting largely of over-milled rice and deficient in the vitamin-B complex as well as in other respects. On the other hand, similar disorders occurred in two of six persons fed on the same diet, but with the addition of extract of rice polishings to provide a supply of vitamin B. So also the same kind of disorders occurred in two of six persons to whom "red" (under-milled) rice was given instead of over-milled rice; the diet of these persons contained considerably more protein as well as vitamin B than that of the seventeen persons fed on the vitamin-deficient diet. These experiments have been claimed as proof that beri-beri is caused by vitamin-B deficiency, but no such claim was made by Strong and Crowell. What the experiments showed was that a monotonous diet consisting chiefly of rice and deficient in proteins, in vitamin-B complex, and in other respects, caused nutritional disorders. They also showed that similar disorders, though of lesser severity were caused by the same kind of faulty diet even when *vitamin-B complex had been added to it.*

Fraga failed to produce beri-beri in persons fed on a diet deficient in the vitamin-B complex. Taguchi (1922) produced symptoms of beri-beri in persons fed entirely on a diet of over-milled rice; numbness of the legs appeared on the fourth day and cardiac dilatation on the fifth day of the experiment, so that the disease was far more likely to have been caused by poison in the sample of rice than by a vitamin deficiency. No deficiency disease has ever been known to appear within so short a time.

(3) The observations of Fraser and Stanton and other workers have shown that when beri-beri occurs in groups of persons living chiefly on over-milled rice the disease can be abolished by changing the diet to one of under-milled rice; but obviously the same thing would have happened if the over-milled rice had been toxic and if a change had been made to any non-toxic rice. Apart from the possibility that the over-milled rice may have been toxic it would certainly have been deficient in other important constituents besides the vitamin-B complex.

(4) Many outbreaks of beri-beri have been reported in which the diets of the affected groups of persons were better supplied with vitamin-B complex than the diets of other groups which remained free from the disease. There have even been outbreaks in institutions in which the diets had been expressly designed to ensure a good supply of the vitamin. This was the case in the outbreaks described by Barrett as occurring in institutions in Sierra Leone in 1931–32; in some of these the disease was controlled by removing the pericarp of the rice that was in use and by discarding the water in which the grain was cooked. Both of these procedures must have removed some of the

new rice crop has been taken into use. Outbreaks may occur at any season if the rice supply has been stored through the previous hot and damp season of the year.

Sex Distribution. The disease is more common in males than in females because males form the great majority in labour forces, prisons, etc., in which outbreaks most often occur.

Age Distribution. The disease rarely attacks children, it becomes increasingly common from about the age of six till adult life. After the age of forty it steadily diminishes in frequency. The infantile form of the disease affects sucklings exclusively.

Rice

Beri-beri is so closely associated with a diet consisting largely of rice that special attention must be paid to this foodstuff. Freshly harvested rice is known in the East as *padi* or *paddy*, the grain is enclosed in a tough husk which gives it some protection against harmful external influences such as moisture, microbic invasion, etc. But even in the form of *padi*, proper storage is essential

Methods of Preparing Rice. After removing the husk the outer tough coating of the grain itself must be removed to make it digestible and to prevent it from becoming rancid. Immediately below this coat lie the outer layers, which contain a larger quantity of proteins, fats, vitamins, iron and phosphorus than the central part of the grain. The value of rice as an article of diet depends on the degree to which the outer layers are retained in the process of preparation.

Four kinds of rice are in common use : these are :—

(1) Raw, home-pounded, rice, from which the husk and a small part of the outer layers have been removed by hand pounding.

(2) Raw, machine-milled, rice, from which the husk and a larger amount of the outer layers have been removed by machinery : this is also known as polished, over-milled, white, or Rangoon, rice.

(3) Parboiled, home-pounded, rice ; this has first been soaked in water for one or two days, then boiled, dried, and pounded by hand, to remove the husk and a small part of the outer layers.

(4) Parboiled, machine-milled, rice ; which has been soaked, steamed, dried, and then passed through a mill to remove the husk and a considerable part of the outer layers. This rice has much the same composition as polished rice, but it differs in the important respect that it loses much less of its vitamins by washing and cooking. On the other hand, it does not keep so well and is less attractive in appearance.

The composition of these four kinds of rice, as stated by Aykroyd, Krishnan and Passmore (1940), is shown in the Table, but considerable variations occur in the machine-milled kinds according to the amount of the outer layers that is removed in the process of manufacture. Special emphasis must be laid on the great losses that occur in washing

Occasional outbreaks have been reported from cold countries, but these have usually been associated with a diet of rice. There have been a few exceptional outbreaks in which there was no evidence that rice had been eaten—for example, among the British troops in Mesopotamia, in Labrador and in some institutions in Europe. These outbreaks suggest that the factors concerned in the causation of beri-beri may, exceptionally, be associated with other articles of diet besides rice. Although beri-beri is almost entirely confined to rice-eaters, there are huge areas of rice-growing countries in which the disease rarely or never occurs: people who grow rice for home consumption are very seldom

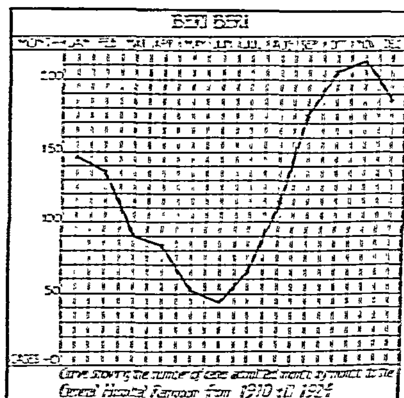


Fig. 41. Diagram of monthly admissions for beri-beri to Rangoon General Hospital, 1910–24.

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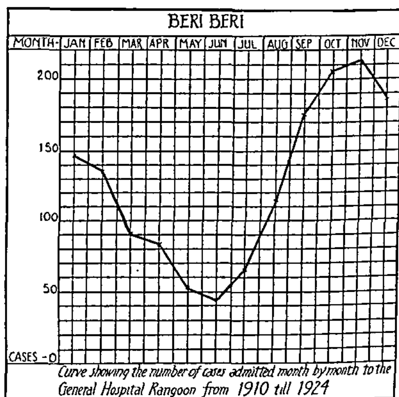


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and cooking ; it will be seen from the Table that there is a great reduction in the calcium, phosphorus, fats and vitamins. The great loss of vitamin B_1 in the washing and cooking of over-milled rice is specially important.

AVERAGE COMPOSITION OF VARIOUS KINDS OF RICE
(Aykroyd, *et al.*)

		Raw		Parboiled		Loss by washing and cooking
		Home-pounded	Over-milled	Home-pounded	Milled	
Proteins (per cent.)		8·5	6·8	8·5	6·4	10%
Fats (per cent.)		0·6	0·4	0·6	0·4	50%
Phosphorus (per cent.)		0·17	0·11	0·28	0 15	50%
Calcium (per cent.)		*0·01*	*0 01*	*0·01*	*0 01*	*50%*
Vitamin B_1 (microgrammes per gramme).	Uncooked	2·4	1·0	2·4	2·2	See next column
	Washed and cooked	1·0	0·2	1·3	1·0	—
Nicotinic acid (milligrammes per 100 grammes)		2·4	1·6	4·0	3·8	40%
Vitamin A		Very little	Trace or nil	Very little	Trace or nil	—

The nutritive value of cooked rice could be greatly increased by rapid rinsing instead of washing and by using the water in which the rice has been cooked as a drink.

The special poverty of cooked raw-milled rice in vitamin B_1 is the probable reason for the great prevalence of beri-beri among persons who live largely on this article of diet.

Apart from the losses that result from cooking, rice is a poor source of calcium, phosphorus, iron, vitamins of the B-group and vitamins A and E ; it is completely devoid of vitamins C and D.

Aykroyd and his colleagues have shown that the addition of small quantities of milk to a diet consisting largely of rice causes a striking improvement in the growth and health of children and experimental animals. The addition of calcium or yeast also causes a considerable, though less striking improvement.

MORBID ANATOMY OF BERI-BERI

After death there are usually inflammatory changes in the mucosa of the stomach and duodenum. In acute cases there may be pin-point hæmorrhages in addition to signs of acute congestion. In the more chronic cases signs of inflammation are not so obvious. The peripheral nerves show degenerative changes of the axis cylinders, which are

usually fragmented in acute cases, while in chronic cases some of the segments of the axis cylinders show signs of degeneration and others are normal in appearance.

The vagus nerve shows similar changes ; so do the nerves of the sympathetic system, though to a less degree. The cells of the anterior horn of the spinal cord are somewhat degenerated.

The changes in the nervous system are remarkably similar to those found in diphtheritic neuritis.

The heart muscle may show degenerative changes. The heart is dilated and hypertrophied as a whole, but the right side is much more affected than the left. The emptied heart weighs, on the average, about 50 per cent. more than the normal organ.

Hydrothorax, hydroperitoneum, hydropericardium and œdema of the skin are usual.

Symptomatology

There are several different types of beri-beri, but the signs and symptoms of every type are those of a toxic polyneuritis. The variations in type depend on (1) the nature and intensity of the agencies concerned in causing the disease, (2) the susceptibility of the persons attacked, and (3) the presence or absence of complicating diseases.

In the early stages of attacks disturbances referred to the alimentary tract are the prominent features ; these consist in a feeling of discomfort in the epigastric region, sometimes accompanied by nausea or vomiting. Then the polyneuritic manifestations make their appearance ; in some cases these are in the form of a peripheral neuritis, but usually there is evidence of damage to the vagus nerves ; this consists in the occurrence of tachycardia, palpitation, dyspnœa and œdema. The two stages of the disease merge with each other, and in very mild attacks the first stage of alimentary disturbance is hardly noticed.

The following types of the disease occur :—

The Mild Type of Beri-Beri

In this type epigastric discomfort may or may not occur. Numbness and tingling in the legs, patches of hyperæsthesia, diminution of the knee jerks, weakness of the legs, and sometimes slight swelling of the feet, may be the only indications of the attack. There must be even milder cases in which the signs and symptoms are so slight that the disease is not recognised.

The Usual Type of Beri-Beri or Wet Beri-Beri

In a typical outbreak several members of a family or community are attacked within a short period. The onset is usually insidious, but it may be rapid or even sudden. At first the patient is troubled with epigastric discomfort and nausea ; sometimes there is actual vomiting,

or there may be diarrhœa. If the temperature is taken it will often be found to be slightly raised. At an early stage the patient begins to feel weak and short of breath. Soon there is tingling or numbness or a feeling of heat, chiefly in the legs. The calf muscles are tender to pressure, the knee jerks are usually rather brisk ; patches of anæsthesia and hyperæsthesia can often be detected on the legs ; the feet begin to swell.

If the onset is gradual and the disease is recognised at this stage it can usually be brought promptly under control by proper treatment. There may even be a spontaneous recovery if the cause of the disease ceases to operate. Usually the symptoms become more severe, the swelling extends to the legs and may affect the whole body, sometimes the serous cavities contain an exudate. Cardiac insufficiency becomes more pronounced owing to dilatation of the right side of the heart. At any stage there may be sudden heart failure. The knee jerks are feeble or absent. Weakness becomes so great that the patient is unable to rise from the squatting posture ; this sign should never be elicited in severe attacks owing to the risk of heart failure from exertion.

If the patient survives, a gradual improvement sets in, but convalescence is slow and it may take months or years for the patient to make a complete recovery. Death is usually from heart failure.

Dry Beri-Beri

This differs from the usual type, (*a*) in the absence of œdema, (*b*) in the greater tendency to chronicity, and (*c*) in the less pronounced degree of involvement of the cardiovascular system.



FIG. 82. Case of dry beri-beri in Philippines. (Graham.)

The gastro-intestinal disturbances are slight or absent, the onset is gradual, wasting and weakness of the muscles are pronounced ; foot-drop and wrist-drop, a high-steppage gait, and loss of the knee jerks, are usual features. Cardiac irritability is moderate in degree or altogether absent.

In untreated or improperly treated cases œdema may occur and so the disease may change from dry to wet beri-beri. So also in wet

beri-beri the œdema may disappear and the disease may assume the dry form. After severe and prolonged attacks recovery is slow and may even be incomplete owing to permanent damage to the nerves. With adequate treatment at an early stage rapid recovery is usual, but in neglected cases the restoration of the function of the nerves is slow.

Acute Cardiac Beri-Beri

This may occur in the form of a sudden exacerbation of the usual type of the disease, but the name acute cardiac beri-beri is more properly given to the attacks in which failure of compensation of the heart sets in rapidly from the onset. There is severe precordial and epigastric distress accompanied by great breathlessness and a rapid feeble pulse. In some cases there is sudden death from heart failure without premonitory signs of disease; more commonly the patient survives for one to five days in great distress. If the patient lives long enough the usual features of failure of the right side of the heart will be observed, such as enlargement of the liver, venous engorgement and rapidly developing dropsy.

Infantile Beri-Beri

Many cases of a severe type of this disease occur among breast-fed infants whose mothers are suffering from beri-beri of a latent type.

In some countries of the Far East in which beri-beri is prevalent many intants die every year of the disease.

The condition is believed to be due to a diminished thiamin-calorie ratio in the milk of the mother not herself apparently unwell. Vitamin B_1 in large doses has a pronounced curative action.

The disease is most frequent in the first three months of the infant's life. The onset is with weakness, pallor, fretfulness, slight fever, and vomiting. These may be the only symptoms in mild attacks and in cases that are treated early, but often the heart becomes severely affected, as is shown by the occurrence of œdema, chiefly of the face and extremities, dyspnœa, aphonia and cardiac enlargement. The knee jerks become feeble or absent.

Other Diseases Related to Beri-Beri

Several types of dietetic neuritis which are more or less closely related to beri-beri have been described; they can be classified provisionally as belonging to "the group of dietetic diseases related to beri-beri."

Ship Beri-Beri is a combination of beri-beri and scurvy and **Pellagroid Beri-Beri** is a combination of beri-beri and pellagra.

The following diseases had previously been recognised but came into prominence because of their frequent occurrence in Japanese prisoner-of-war camps in 1942–45. The diets of the prisoners were

grossly faulty in many and various respects and beri-beri was highly prevalent.

Cerebral Beri-Beri or Wernicke's Encephalopathy is believed to be caused by acute vitamin B_1 deficiency. Several outbreaks occurred in the camps and about 50 per cent. of the patients were suffering also from classical beri-beri. The onset often followed, or was associated with, an attack of dysentery. Anorexia was followed by vomiting, nystagmus and ataxy. Apathy, insomnia, amnesia and sometimes stupor or coma were features of the illness, which was often fatal. Full doses of thiamin given by injection were found effective.

Retrobulbar Neuritis was not uncommon in the camps ; it often followed, or was associated with, the burning-feet syndrome described below, and like that condition was regarded by some observers as being more closely related to pellagra than to beri-beri. Thiamin alone was ineffective as a treatment.

Burning-Feet or Painful-Feet Syndrome was common in the camps. The most prominent symptom was distressing burning pain in the feet, worse at night. There was ascending analgesia of the feet and legs ; the knee jerks were exaggerated at first but usually diminished and finally were lost.

Other names like **Camp Dizziness** and **Spinal Ataxy** were given to forms of dietetic neuritis whose chief features are indicated by the names.

DIAGNOSIS

Typical outbreaks are easy to recognise ; the occurrence of a number of cases of dietetic neuritis which conform to one of the clinical types just described, especially if the diet has consisted largely of over-milled rice, presents a well-defined picture.

In isolated cases other causes of similar symptoms such as poisoning by lead or arsenic, diabetes, and cardiac or renal disease, must be excluded.

The differential diagnosis from epidemic dropsy may be very difficult, this will be discussed in connection with that disease.

Diarrhœa and dysentery which often occur at the onset of attacks of beri-beri have frequently been mistaken for infective forms of these diseases and treated accordingly, with unfortunate results.

Famine œdema differs from beri-beri in occurring on a starvation diet and in the combination of œdema with polyuria and cardiac depression ; various combinations of the two diseases are not infrequent.

Prognosis. The severity of the disease varies within wide limits. In some outbreaks the mortality has been as high as 60–70 per cent. : but even apart from proper treatment the case mortality seldom rises above 30 per cent. ; in mild outbreaks it is almost negligible. If the patient has come under proper treatment at an early stage, the disease is very amenable to treatment and can usually be arrested within a few

days. Outbreaks also are easily brought under control when properly handled.

When the heart is greatly dilated the outlook is grave, even with energetic treatment. In the chronic dry form of the disease, if serious damage has already been done to the nerves, recovery is slow, and may never be complete. One attack predisposes to others: those who have suffered from a severe form of beri-beri would be well advised to avoid a diet of rice for a prolonged period, or at all events to cut down their consumption of rice and use more wheat and other nutritive articles of diet.

TREATMENT

The rules for the treatment of beri beri and related diseases are:—

(1) Give a protein-rich diet with all the vitamins added, plus high doses of vitamin B_1.

(2) If possible cut out rice from the diet for a time and in any case ensure that any rice taken is fresh, uncontaminated and not over-milled. Omission of rice for a time may alter the intestinal flora.

Fresh milk and orange juice are suitable when there is gastro-intestinal trouble. Patients who can digest solid food ought to have milk, eggs, green leafy vegetables, wheat and legumes. Rice even when sound, may aggravate the symptoms. Cases of disease resembling beri-beri have been reported as being caused by edible oils which have become contaminated by poisonous substances or have developed toxins through fermentation.

By a complete change of diet and the provision of an ideal diet the patient is safeguarded against every likely cause of clinical beri-beri.

Thiamin hydrochloride (vitamin B_1) should be given in severe cases in doses of 1–3 mg. thrice daily by the mouth; for heart failure intramuscular injections of 5-50 mg. have been given with dramatic success in many cases. This drug is costly and the less expensive concentrated extracts of rice polishings, such as *tiki-tiki* are adequate in most cases. Marmite, Bemax and brewer's yeast are also valuable.

All the other forms of treatment should be directed towards dealing with the special conditions which exist. Complete rest in bed is essential to guard against heart failure; mild saline purgatives are useful; digitalis is often prescribed, but is of very doubtful value.

In cases of dilatation of the heart, free blood-letting may save life; it should be resorted to when there is distension of the veins of the neck and cardiac distress.

Alcohol is specially harmful; it causes a neuritis very similar to that seen in beri-beri. Arsenic is objectionable for the same reason.

In the chronic neuritic type of the disease, rest and nourishing diet are needed; massage and passive movements should be carried out when the acute stage has passed off. Postural treatment may be necessary to prevent deformities.

Special attention must be paid to the diet of unaffected members of families or institutions when an outbreak is in progress.

The treatment of infantile beri-beri is on the same lines; the immediate removal of the infant from its mother's breast is essential. An intramuscular injection of thiamin hydrochloride, 2–5 mg., should be given at once in very severe cases, and repeated if necessary on the two or three following days.

Concentrated extracts of rice polishings have a great reputation both in treatment and prevention. A diet of milk, suitable to the age of the infant, with a little orange juice and cod-liver oil, should be given.

PREVENTION

The general principles laid down for treatment apply with equal force to prevention. Over-milled rice should not be used.

Rice should be manufactured and stored in conditions which protect the grain against moisture and heat. The grain should be kept in a dry, cool, and well-ventilated, storehouse; the period of storage should be as short as possible.

Any stock of rice which is suspected of causing beri-beri should be discarded and used only for feeding animals: the store-room in which the rice has been kept should be emptied out, whitewashed or disinfected and then kept empty for several weeks before being used again.

Rice in transit is often exposed to wetting; if this occurs the rice should be thoroughly dried as soon as possible.

These precautions protect the users of rice against the possibility of being poisoned by damaged rice; they are also eminently rational from the point of view of preserving the nutritive properties of a grain which forms the chief article of diet of many millions of people.

Edible oils used in cooking must be regarded as possible sources of intoxication.

Insistence on a diet rich in vitamins as well as all the other constituents of a wholesome diet is rational on general as well as special grounds. In addition to being a poor source of vitamins, rice is deficient in available proteins, and therefore ought to be supplemented by articles of diet which are more nutritious.

Soya beans and other leguminous seeds are considered to have a great protective value against beri-beri. When these are available they ought to enter into the diet of labour forces and other communities likely to be attacked by the disease.

Person-to-person infection is a very remote possibility as a causative factor, but intestinal infections are important in predisposing to the disease, and therefore attention should be paid to the hygienic conditions of the houses or institutes concerned.

When outbreaks occur among persons living on a rice-free diet, it is desirable to eliminate all articles of food which fall under suspicion,

such as preserved and tinned foods, ship's biscuits, preserved or decomposed fish, etc.

Those who have not lived in rice eating areas in the tropics often do not comprehend the reality of food bigotry. To many millions the words " food " and " rice " are synonymous and even when death from famine is imminent some prefer extinction to life on wheat or other cereal food. Where firewood is scarce the issue of wheat in rice famine areas has demonstrated the almost insoluble problem of cooking it. Rice is easily cooked with a minimum quantity of fuel. One of the cheapest and most important health giving measures which any local authority can undertake is instruction in the death dealing qualities of polished milled rice. Many commercial firms and large estate owners issue thiamin enriched milled rice to their employees. This is a second best solution to what is primarily an educational problem but it may serve as a stop gap.

(2) PELLAGRA

The name pellagra comes from two Italian words, *pelle* (skin) and *agra* (rough).

Definition. The commonly accepted definition is " a disease caused by deficiency of nicotinic acid in the diet." The accuracy of this definition is open to doubt ; the exact cause or causes of the disease cannot be stated with certainty, so that it is safer to define the condition in general terms as follows . the name pellagra is applied to a dietetic disease which is specially common in communities whose diet consists largely of maize. The disease varies greatly in its clinical features ; there is nearly always some degree of glossitis and stomatitis ; usually there is a special type of dermatitis ; gastro-intestinal disturbances, mental symptoms, and neuritis, often occur. Nicotinic acid has a pronounced curative action, but in many cases riboflavin or vitamin B_1, or both of these vitamins, are also needed to control the disease.

The disease has no uniform pathognomonic feature, its exact cause or causes cannot be stated with certainty so that a precise definition must await further knowledge.

History. From 1680 to 1700 the disease was first described in Spain where pellagra is believed to have made its appearance shortly after the introduction of maize as an article of food.

In 1762 Gasper Casal, a Spanish physician, wrote the first satisfactory account of the disease.

By 1776 the disease had assumed such proportions in Italy that a special inquiry was made in Venice, and the sale of unsound maize was prohibited by law.

In 1814 Guerreschi held that just as ergotism is caused by ergot of rye, so also related moulds in maize may produce pellagra.

In 1871–84 the disease became very common in Italy, more than 100,000 cases being recorded in one year.

In 1907 the disease was recognised as being common in the southern parts of the United States of America. It may have existed for many years before that time without being detected.

Geographical Distribution. Just as beri-beri is almost confined to rice-eaters, so pellagra is mainly a disease of maize-eaters.

In Italy the disease used to be terribly common, but there has been a steady fall in the number of cases since 1900. Deaths have declined from 4,000 to less than 100 yearly.

In Roumania pellagra was first seen in 1910 ; its spread is said to have corresponded with the introduction of maize carried in small coasting steamers and often damaged by water in transit. In 1918 there were 70,000 cases.

There were about 150,000 cases and more than 10,000 deaths in the Southern States of the U.S.A. in 1916. The incidence of the disease increased till 1928 and then began to diminish rapidly so that now the *deaths are relatively few.*

The disease is prevalent in the Balkan States, Turkey, Greece, Spain, Portugal, Egypt, Mexico, Brazil, Argentina and Jamaica. Cases occur in most of the countries of the world ; they are nearly always associated with a diet of maize. Mild, atypical and unrecognised, attacks are probably more common than is generally realised. The disease attacks chiefly the poorer labouring classes of the affected countries.

Seasonal Distribution. The symptoms are usually most prominent during the spring and early summer.

Sex and Age. Females are more often attacked than males ; an infantile form of pellagra affects sucklings, who are believed to get the disease from their mother's milk. The symptoms are stomatitis, pyorrhœa and general ill health. Typical lesions are rare in infants but common in childhood.

ÆTIOLOGY

If the word maize is substituted for the word rice, most of the statements made about the causation of beri-beri apply equally to pellagra. Some of the theories as to the cause of pellagra are as follows :—

Maize-Intoxication Theory. Lombroso (1872) and several later observers brought forward strong arguments in favour of this view, which is supported by the following facts : (*a*) the distribution of the disease corresponds closely with that of maize ; (*b*) there is evidence that maize which has been damaged during storage is specially liable to cause the disease ; (*c*) explosive outbreaks often occur (a personal statement to this effect was made to the writer by Professor Goldberger) ; (*d*) Stockman has isolated a toxin from maize which caused the same changes in the nervous system of monkeys as are found in human pellagra. These changes were caused even

when the animals were fed on a generous diet of milk, butter and fresh fruit.

Harriette Chick has also brought forward evidence in favour of the view that pellagra is an intoxication, though vitamins may be curative by acting as antidotes to the causative toxin.

The Protein Deficiency Theory. Wilson argued that the available proteins of maize are of poor quality and that malnutrition results from their use.

Amino-acid-Deficiency Theory. Goldberger and Tanner suggested that the deficiency did not apply so much to the proteins as to certain amino-acids which are essential to nutrition.

Alimentary-Tract-Infection Theory. The Thompson-McFadden Commission attached some importance to intestinal infection as a probable factor, but the evidence was inconclusive, and the view does not fit in with the known facts connected with the ætiology of the disease.

Vitamin-Deficiency Theory. As in the case of beri-beri, this is the theory which has most supporters at the present time. The view was first proposed by Funk in 1913. Goldberger, Chittenden, and others, have produced a disease in dogs, monkeys, and rats, which has many points of similarity to pellagra. Goldberger believed that there was a "pellagra-preventing factor" (vitamin P.P.) in healthy diets, and that deficiency of this was the cause of the disease. McCollum criticised the experimental diets used by Goldberger, and pointed out that they were deficient in available proteins, salts and vitamin A, as well as in the pellagra-preventing vitamin. It is also noteworthy that the experimental diets employed by Goldberger contained maize, so there is a possibility that some positive factor in the maize, rather than the absence of a special vitamin, may have caused the disease in the experimental animals. Shattuck, who investigated the diets of 144 patients, could not find any evidence of vitamin deficiency in 58 of them. T. D. Spies actually observed definite improvement in several patients who were being fed on a "pellagra-producing diet."

J. A. Kooser (1939) found that all but 3 of 39 patients had taken moderate quantities of fresh milk, meat or vegetables; 24 had received good or even generous supplies of one of these articles of diet.

W. R. Aykroyd and N. Swaminathan (1940) found that the diets of communities affected with pellagra contained more nicotinic acid than the diets of the poorer classes of rice eaters in India who remain free from the disease.

A. Clarke (1941) states that pellagra is common in West Africa among persons who live largely on cassava (manioc), which is rich in the vitamins of the B_2 group. He suspects that the disease is caused by a toxic glucoside contained in cassava (see also page 487).

The Combined Intoxication and Vitamin-Deficiency Theory. As in the case of beri-beri, the only hypothesis on which all the known facts

can be explained is that certain articles of diet contain a poison, or in the process of metabolism give rise to a poison, which causes the disease but which can be neutralised by nicotinic acid (the essential constituent of Goldberger's P.P. factor). The close association of pellagra with a diet consisting largely of maize strongly suggests the existence of a toxic factor which is specially likely to exist in, or to be derived from, maize. The pronounced curative action of nicotinic acid equally suggests that the poison can be neutralised by this vitamin.

This theory has been strongly hinted at in the following remark by the experts of the Medical Research Council in the book on "Vitamins" (1932): "the action of the P.P. factor might be to neutralise a toxin rather than to make up a deficiency, just as vitamin D neutralises the anti-calcifying effect of certain cereals, though it also makes up a deficiency."

There are other striking points of analogy between pellagra and beri-beri. The general features of the two diseases are very similar. Each has an initial stage which suggests the action of a poison which irritates the gastro-intestinal mucous membrane. This is followed by a stage in which there is damage to the nerves and other tissues suggestive of the action of a poison. The successful treatment and prevention of both diseases follow the same general lines. As in the case of beri-beri most workers now attribute pellagra to an upset of intracellular enzyme mechanism by specific deficiencies in enzyme-making material. Pellagra in typical cases is a well defined entity but there are numerous grades and shades of this clinical condition and many are of opinion that a multiple vitamin-B complex deficiency, especially of nicotinic acid, coupled with a relative lack of high class proteins and an overlay of infection or lowered vitality is needed to produce the typical clinical picture.

Morbid Anatomy. There is wasting and degeneration of the muscles, including the cardiac muscle. Fatty and cirrhotic changes of the liver and kidneys are common. The affected parts of the skin show the changes which were present during life; these are of an inflammatory and atrophic type.

The mucosa of the small intestine is wasted, sometimes also ulcerated. The neurons of the whole nervous system are degenerated, especially those of the anterior horns of the spinal cord and the sympathetic system.

Symptoms. These are very variable, but the disease conforms to one general type; gastro-intestinal disturbances occur in the early stages and are followed by symptoms due to degenerative changes in the nervous system.

The severity of the disease has a wide range: some cases are so mild as to be almost unrecognisable, others are rapidly fatal; with the exception of the latter the course of pellagra is chronic with pronounced "ups and downs."

Mild "Sub-clinical" Pellagra

In places where pellagra is prevalent many persons have poor appetites, indigestion, low intelligence, soreness of the lips and tongue, and general debility.

Many of these patients' show characteristic symptoms of fully developed pellagra at a later stage.

Typical Pellagra

After suffering for weeks or months from the symptoms just described, some of the patients gradually become worse: the tongue becomes red and glazed, the mucosa of the mouth is slightly inflamed, patches resembling sunburn appear on the backs of the hands, sometimes also on the back of the neck, the arms, cheeks, or nose. Gradually these patches become rough, dark red, or even blackish, and the condition resembles scaly dry eczema. The parts chiefly affected are those exposed to sunlight: the ultra-violet rays act as irritants to the skin which is already damaged either by the toxins generated in the course of the disease or by deficiency in nicotinic acid or by a combination of these two factors.

Some observers hold that toxins are actually formed in the skin by the action of light on precursors of the toxins which circulate in the blood stream. Against this view is the fact that in some cases the dermatitis affects the arm-pits, flexures of the elbows, perineal or perianal regions which are subjected to friction or to pressure by clothing. Irritation by ultra-violet rays may account for the pronounced tendency of the dermatitis to become worse in the spring and early summer, and to improve during the cold dark months of the year.

In most of the cases the backs of the hands are affected either alone or at the same time as other parts of the body.

When the dermatitis begins to appear there is usually an exacerbation of the gastro-intestinal symptoms, the tongue becomes redder and more glazed, there is stomatitis with salivation and burning of the mouth; epigastric discomfort increases, often accompanied by flatulence. Some mental deterioration is usually noticed: this takes the form of confusion of thought, depression or melancholia; insomnia is common. Fleeting pains in the limbs, tremors of the tongue and muscles, progressive weakness, and exaggeration of the knee-jerks, are sometimes observed. Paræsthesiæ and burning sensations in the palms and soles may occur. Anæmia is usual.

The relative frequency of the symptoms is shown by an analysis of 73 typical cases in one outbreak. There was soreness of the lips and tongue in all, dermatitis in 56, mental symptoms in 51, diarrhœa in 40, urethritis in 27, severe vomiting in 24, peripheral neuritis in 23, vaginitis in 23 and proctitis in 21.

The Severe Type

This usually appears as an aggravation of the previously described types, taking months or years to develop, but occasionally the disease sets in rapidly. The symptoms become progressively more severe; mental and physical deterioration are the most prominent features. The patient often suffers from delusional, maniacal or depressive insanity, and ends his days in a lunatic asylum. Such cases have been more common in the southern United States of America than in European countries. Fortunately, they constitute only a small per-



Fig. 83. Pellagra, showing eruption on face, neck and hands. (Dr. MacDonald.)

centage of all the cases. In some of the severe attacks periods of fever and prostration occur; the name "pellagra typhus" has been given to cases of this kind.

Aberrant Types

Certain types of dietetic disease occur which are regarded by some observers as forms of pellagra, and by others as distinct diseases. A final decision with regard to the classification of these conditions cannot be made till further light is thrown on their exact causes, and on the cause of pellagra itself. The name pellagra should not be applied, without the addition of some qualifying word, to doubtful cases or

outbreaks which do not conform to the clinical picture of pellagra as already described, especially if the diet of the patients has contained little or no maize.

Reference will be made later in this chapter to dietetic diseases which resemble pellagra in certain respects.

Course of the Disease

This is usually slow, lasting from two to fifteen years or even longer. Exacerbations in spring and summer alternate with remissions in the late autumn and winter.

Unless proper treatment is carried out the general tendency of pellagra is to become worse, but many cases remain mild and gradually recover without having severe symptoms at any time. Adequate treatment can arrest the progress of the disease in the early stages, but the advanced forms are very intractable; permanent damage has already been done to the nervous system and recovery cannot be expected; but even insane patients may show considerable improvement in their physical condition when properly treated.

Complications. Other dietetic diseases often occur as complications of pellagra; among these are—scurvy, night-blindness, keratomalacia, nutritional anæmia, beri-beri and ariboflavinosis. The last-named disease has often been confused with pellagra because of the striking benefit which has resulted from treatment with nicotinic acid. In some outbreaks the symptoms have been so suggestive of beri-beri that difficulty has arisen in deciding which of the two diseases was present.

Prognosis and Mortality. Convalescence is always slow in prolonged and severe forms of the disease. Those who have once suffered are very liable to further attacks unless the causal factors are eliminated. Alcoholics do badly; so do old people and those who suffer from intercurrent malaria or dysentery. The case mortality in Italy is only about 3–5 per cent., while in the United States of America it has been as high as 30 per cent. in certain localities.

In Italy 5–10 per cent. become insane; in America as many as 40 per cent. of the severe cases end their days in mental hospitals.

Diagnosis. In the milder forms it may be impossible to make a definite diagnosis, but pellagra should always be suspected as being the probable cause of any vague dyspeptic or nervous symptoms which occur in persons living in pellagra zones. On the other hand, mistakes are often made by attributing all such symptoms to pellagra in localities where the disease is prevalent. The proper attitude is to suspect pellagra and act accordingly, but at the same time to make a careful investigation of the patient to make sure that there is no other cause for his symptoms.

The diagnosis is usually regarded as justified when two of the following three features occur: (1) soreness of the lips and tongue; (2) the characteristic skin lesions; and (3) mental or other symptoms

referable to the nervous system and of the types described. Important points are : (1) the occurrence of other cases in the same locality ; (2) the previous diet of the patient ; (3) the occurrence of seasonal variations in the signs and symptoms ; (4) the prolonged "up and down" course of the disease ; (5) the symptoms ; (6) mental deterioration in a person living in an endemic area ought to arouse suspicion of pellagra.

Differential Diagnosis. The disease most often confused with pellagra is ariboflavinosis (*see* p. 477) which is cured by a related vitamin of the B_2 group, riboflavin. The skin and nerve lesions of pellagra are different.

Sprue is distinguished by the characteristic type of diarrhœa and the absence of the special skin and nerve lesions. Symptoms suggestive of beri-beri are often seen in pellagra, in such cases there is likely to be a combination of the poisons or vitamin deficiencies which cause the two diseases.

Treatment

The essential treatment is dietetic. The diet must be nutritious and specially rich in high-grade proteins and all the vitamins. Fresh milk is eminently suitable as the foundation of the diet ; such articles as fresh meat, liver, eggs, fresh fruit, potatoes, green vegetables, wheat, peas and beans are of value. A very important point is to exclude maize in every form from the diet.

Nicotinic acid has a strikingly curative action ; the usual dose is 0·1 gm. five times daily by the mouth for ten days, but larger doses may be needed in severe cases.

When prompt benefit does not follow, other vitamins should also be given in full doses, especially vitamin C, vitamin B_1 and riboflavin.

D. C. Sutton (1940) has recorded two cases of clinical pellagra in which nicotinic acid together with riboflavin, liver extract and a good diet failed to cure, but extract of pituitary gland was effective.

The patient should be kept at rest in healthy surroundings, he should have plenty of fresh air, avoiding exposure to sunlight. A cool climate, cheerful company and hopeful suggestion help to promote recovery. Alcohol is contra-indicated. Iron is of special value, it can be given in the form of large doses of Blaud's pills.

Symptomatic treatment is needed for any special manifestations which may occur.

For dermatitis, avoid greasy applications ; calcium dusting powder is suitable.

For stomatitis a weak permanganate of potash mouth wash is useful.

A diet of fresh milk and large doses of dilute hydrochloric acid are recommended as being the best means of controlling the diarrhœa of pellagra.

Infantile pellagra is treated by taking the child away from the mother's breast and giving a diet of fresh, unboiled milk. The juice of

an orange or a corresponding quantity of other antiscorbutic substance must be given daily if boiled or condensed milk has to be used. Nicotinic acid is given in doses of 10 mg. every two hours.

Prevention consists in supplying a suitable diet rich in all vitamins and in high-grade proteins. Fresh milk is of special value. The use of maize should be restricted or prohibited altogether when the disease is prevalent. Yeast is valuable as a preventive.

In the last century the French physicians carried on an active campaign for the elimination *of maize as an article of diet : the prompt* disappearance of pellagra from France appeared to be a complete justification of this policy. Attention should be paid to the proper storage of maize. In Italy the compulsory use of drying machines in bakeries has met with great success.

Mothers who suffer from pellagra should not be allowed to suckle their infants.

(3) ARIBOFLAVINOSIS

Much attention has been paid during the past few years to a dietetic disease of which the chief features are angular stomatitis, soreness of the tongue, cheilosis (redness, desquamation and ulceration of the lips), scrotal dermatitis and vascularisation of the cornea. Sore throat, dysphagia, hoarseness and aphonia have also been noted. The condition rapidly responds to treatment with brewer's yeast, Marmite or riboflavin. Failure of vision with increasing difficulty in reading was noted in prisoner of war camps in Asia during the recent war. Pallor of the temporal halves of the optic discs with constriction of the visual fields was found. Retrobulbar neuritis was probably the underlying lesion, and was accompanied by various signs of interference with the integrity of the nervous system such as Rombergism, pins and needles feelings in the limbs and painful soles of the feet especially at night. Riboflavin proved to be the best remedy although nicotinic acid was a most valuable adjunct when diarrhœa and paræsthesia were troublesome.

ANÆMIAS ASSOCIATED WITH FAULTY DIETS OR THE NUTRITIONAL ANÆMIAS

The nutritional anæmias, including "the anæmia of pregnancy," are clearly associated with certain faults which are specially common in the diets of the inhabitants of tropical countries. In these anæmias two or more causes are often at work simultaneously and in varying degrees of intensity so that corresponding variations occur in the clinical picture.

The student and practitioner need not be unduly depressed about the complexity of the problem ; the practical handling of cases will seldom give rise to serious difficulty provided that a careful investiga-

tion is made of each patient. A close enquiry should be made into the previous diet, illnesses, and mode of life ; this, with a complete physical examination, including the use of the usual laboratory methods of blood examination, will nearly always give clear indications of the appropriate treatment.

Hæmopoiesis

The transport of oxygen and of carbon dioxide in the body is greatly influenced by the number of red blood cells and by their hæmoglobin content. In the tropics anæmia is almost universally present in indigenous peoples. A 10 per cent. Sahli reading is not uncommon in South India in persons still trying to work. Classical pernicious *anæmia (Addison) due to lack of Castle's intrinsic factor is rare in the* tropics but every other variety of nutritional anæmia is found complicated by the effects by protozoal, helminthic and other noxious factors associated with tropical infections. The process of red blood cell manufacture (hæmopoiesis) which takes place in the red bone marrow is not yet fully understood but it is believed that deficiency in certain dietetic factors which include vitamin B components such as pteroylglutamic acid (folic acid) and vitamin B_{12} results in the red cells developing in an abnormal manner from megaloblasts so that the average size of red blood cells released into the circulation is larger than normal, *i.e.*, the anæmia is macrocytic.

On the other hand deficiencies in mineral nutritional components, especially iron, and constant blood loss on account of piles, ulcers or ancylostomes results in blood manufacture in the physiological normoblastic manner with cells of normal size or less though deficient in number, and so to a normocytic or microcytic anæmia.

As both mineral and vitamin deficiencies may operate simultaneously the resulting average size of corpuscle will depend on whether the megaloblastic or normoblastic method of formation predominates. Trowell's suggestion of the name dimorphic anæmia is a useful one for such a condition which is very common.

Macrocytic Nutritional Anæmia

Definition. A severe and often fatal anæmia of a macrocytic type which occurs in both sexes, but in women is chiefly found in the second half of pregnancy ; it is associated with a seriously deficient diet and responds to large doses of liver extract or Marmite.

History. Severe " anæmias of pregnancy " have long been known to be common in many places in the tropics.

In 1932 Lucy Wills, working in India, found that this was usually a megalocytic (macrocytic) anæmia which often showed a severe exacerbation in the seventh or eighth month of pregnancy ; premature labour usually followed and the patients either died or made a rapid recovery.

Marmite, in doses of 30 gm. daily, caused striking improvement in

most cases; liver extracts in the doses usually prescribed for pernicious anæmia were less effective.

Ætiology. The disease occurs only in persons whose diets are seriously defective: high grade proteins, fats, vitamins, calcium and iron are usually inadequate

The results of treatment show that the causal agency, whether a toxin of metabolic origin or a deficiency, can be neutralised by factors contained in liver or Marmite (autolysed yeast)

Women in the second half of pregnancy are specially prone to the disease, but it also occurs occasionally in non pregnant women.

Malaria is a strongly predisposing factor in the cases which show a tendency to hæmolysis. Hook-worm infection and other conditions conducive to anæmia increase the susceptibility to the disease.

Symptoms. The patients are obviously very anæmic: they complain of weakness, palpitation, giddiness and loss of appetite.

Syncopal attacks are common there may be irregular fever and gastro-intestinal disturbances

The skin is pale and often has a lemon-yellow tint.

In the case of the hæmolytic type the spleen is enlarged and there may be a tendency to jaundice Petechial eruptions of the skin or other signs of a hæmorrhagic tendency occur in about 25 per cent. of these cases.

The red blood corpuscles are greatly reduced in number, ranging from ½ to 2½ million per c.mm.: the average count is 1 to 1½ million.

The average size of the corpuscles is larger than normal.

The hæmoglobin is much reduced, though not to the same degree as the red blood corpuscles so that the colour index averages 1·3: it may be as high as 1·7, but in exceptional cases it is as low as 0·9.

H. Fairley found that the blood of the newly-born infants of patients was quite normal; evidently the fœtus absorbs its full ration of nourishment in spite of the impoverished condition of the maternal blood.

The drain on the mother's blood is greatest during the period of rapid growth of the fœtus so that a sudden intensification of the anæmia occurs in the seventh or eighth month of pregnancy; this results in premature labour, and either the death of the mother or a rapid improvement in her condition.

The death rate is very high, about 40 per cent. in untreated cases; even with energetic treatment at an early stage there is serious risk to life.

Treatment. The less severe cases respond well to autolysed yeast —such as Marmite—by mouth. Marmite is expensive and it is cheaper and quicker to give intramuscular injections of a potent but not too refined liver extract. In severe cases a large initial injection should be followed by daily maintenance doses till the patient is out of danger. Blood transfusion should be reserved for really desperate cases. On general principles it is well to use a relatively crude liver product but

Anahæmin—*a highly refined product*—does act powerfully in these cases and completely changes the bone marrow picture in a few hours. It may usefully be employed to check the potency of some of the crude liver extracts of local manufacture on sale in tropical bazaars. One well known liver extract contains added riboflavin and owes its superiority over some other brands to that addition. An easily digested protein-rich diet should be given. Specific treatment should be continued till the blood count and hæmoglobin level are normal. Folic acid and vitamin B_{12} (Cytamin) are effective in tropical megalocytic anæmia. Their employment in these cases will be determined by the relative expense of the various remedies available.

Diagnosis. This is easy in typical cases. True pernicious anæmia is very rare in the tropics. Histamine-fast achlorhydria is always found in true pernicious anæmia, but is also quite common in nutritional macrocytic anæmia as indeed it is in microcytic ancylostome anæmia. Its only value in differential diagnosis lies in the frequent return of normal gastric secretion which often occurs when dietetic and iron-deficiency anæmias improve. In pernicious anæmia the histamine-fast achlorhydria is permanent. Even in profound macrocytic nutritional anæmia involvement of the posterior columns of the spinal cord (with loss of vibration sense) does not occur.

Microcytic and Normocytic-Nutritional Anæmia

This is very common and is due to deficiency of iron in the diet often combined with blood losses by hookworm infection. The colour index is low. Large doses of iron—Ferr. et Ammon. Cit. 90–120 grains a day or 45–90 grains Blaud's pill or 30 grains of ferrous sulphate produce prompt and steady improvement. It is likely however that if the diet is grossly deficient in iron attention should also be paid to the protein and vitamin content.

Much money is wasted in the tropics, especially in the cities by the prescription of expensive vitamin and liver preparations for patients who require only a few coppers' worth of ferrous iron to restore them to health. Too often the money wasted on injections would be better spent on good protein food, or on fruits, seeds and vegetables. Pregnant women especially need a more generous diet than others ; the fœtus abstracts a full ration of nourishment so that if the reserves in the maternal blood are low disaster is bound to follow. This applies especially to protein, vitamins and iron.

OTHER DISEASES ASSOCIATED WITH FAULTY DIETS

Epidemic Dropsy

Since 1877 the name epidemic dropsy has been given to a special type of dietetic disease which occurs chiefly in Calcutta and neighbouring parts of Bengal, and to a less extent in other parts of India. In

its symptomatology and epidemiology the disease resembles beri-beri in many respects, so that it has been widely regarded as a special type of that disease.

The disease is now regarded as a dietetic intoxication caused by poisons contained in argemone oil which often occurs as an adulterant of the mustard oil used in cooking. According to this view the disease would be defined simply as "argemone-oil poisoning" or "argemonism."

History. The name epidemic dropsy was first given to the disease in 1877 by K. McLeod, who described severe outbreaks in Calcutta and concluded that the disease was not beri-beri but an infection communicable from man to man. His chief reason for regarding the disease as infectious and therefore "epidemic" seems to have been the occurrence of outbreaks in Assam and Mauritius shortly after the arrival of coolies who came from Calcutta where many cases were occurring at the time. In the light of present knowledge it is likely that the outbreaks were caused by food sent from Calcutta to these places.

Distribution and Epidemiology. More cases have occurred in Calcutta and its suburbs than in all other places taken together. Great outbreaks were recorded from Calcutta in 1877–80, 1909, 1916 and 1926. In the 1926 outbreak at least 6,000 cases occurred with about 1,200 deaths.

Smaller scattered outbreaks occur every year in Calcutta and other places in Bengal, occasionally also in other parts of India and elsewhere, but almost invariably in communities which had imported food from Bengal or neighbouring parts of the surrounding provinces.

Outbreaks may occur at any season, but far more cases originate between the middle of June and the middle of November than during the rest of the year. The seasonal prevalence corresponds very closely with that of beri-beri in Japan and Burma.

Both sexes are equally affected; infants apparently escape altogether, and young children are seldom attacked. Isolated cases are rare; the disease occurs in outbreaks in which attacks appear within a short period in a varying proportion of the members of a community living on the same diet or eating some article of food from the same source of supply.

Towns, large villages, institutions, labour forces and families are the units of population most frequently affected.

Europeans and other groups of people who eat little rice and mustard oil are rarely attacked.

Ætiology. The condition is now accepted as being due to poisoning by the seeds of the Mexican poppy (*Argemone mexicana*).

The work of R. B. Lal, R. N. Chopra, C. L. Pasricha, and others, in Calcutta has shown that oil expressed from the seeds of *Argemone mexicana* frequently occurs as a contaminant of mustard oil which

is widely used as an article of food in Bengal, and that symptoms suggestive of epidemic dropsy are caused by feeding human volunteers or experimental animals on a diet containing argemone oil. The mustard oil used by the affected persons in a number of recent outbreaks was found to contain 1–10 per cent. of argemone oil.

Symptoms. In some outbreaks the symptoms are so similar to those of beri-beri that it may be difficult to detect any clinical differences between the two diseases. In other outbreaks, especially those of great severity, there are certain features which are distinctive of epidemic dropsy.

Incubation Period. The action of the poison is cumulative so that when the daily dose is small symptoms may not appear till the toxic food has been used for a considerable time, but a few cases have been recorded in which the incubation period seems to have been as short as one or two days. The incubation period cannot usually be determined with accuracy.

Onset. This is insidious in mild cases, but it may be rapid or even sudden in severe attacks. The earliest symptoms are usually swelling of the feet, fever, gastro-intestinal disturbances, palpitation, and dyspnœa ; sometimes the only symptoms are swelling of the feet and weakness.

Relative Frequency of the Symptoms. Apart from œdema which in varying degrees of severity, always occurs, there are pronounced differences in the symptoms, not merely in separate outbreaks, but also in individual cases in the same outbreak.

This variability is shown by the following figures taken from the accounts of several outbreaks by different observers. Œdema was noted in 100 per cent. of the cases in all outbreaks ; fever in 30–60 per cent. ; gastro-intestinal disturbances in 20–80 per cent. ; palpitation in 15–90 per cent. ; dyspnœa in 7–60 per cent. ; tenderness on pressure over the calf muscles in 25–50 per cent. ; increase in the knee jerks in 7–70 per cent. ; loss of the knee-jerks at some stage in 5–55 per cent. ; vascular mottling of the skin of the legs in 10–28 per cent.

Increase of the knee-jerks is most often noted early in the course of the attack, not infrequently this is replaced by diminution or complete loss of the jerks at a later stage. Glaucoma is not uncommon, either as a complication or a sequela of the disease. The vascular mottling results from dilatation of the capillaries, which may be so pronounced as to cause the formation of growths resembling sarcoids.

A tendency to hæmorrhages has been observed in some outbreaks ; hæmorrhagic retinitis occurred in a small outbreak seen by myself. Some degree of anæmia is usual. Intense anæmia has been reported in a few severe attacks.

Course of the Disease. There is usually a gradual increase in the severity of the symptoms, a rather prolonged illness and slow convalescence. The disease varies in severity, from the mildest attacks in which

there is only slight swelling of the feet to the most severe cases with death in a few days, usually from heart failure.

Sudden death from heart failure may occur in patients who have had no symptoms before the attack.

Diagnosis. The disease resembles wet beri-beri in the following respects: (1) Its close association with a diet of rice; (2) its occurrence as outbreaks in which a number of persons eating some common article of diet are affected; (3) its seasonal distribution is very similar to that of beri-beri in Japan and Burma; (4) œdema, gastro-intestinal disturbances, cardiac symptoms, and the course of the disease, are common features of both conditions. It differs from beri-beri: (1) In showing a less degree of peripheral neuritis in most cases; (2) in being specially associated with a diet containing mustard oil; (3) in the frequent occurrence of glaucoma and a pronounced mottling of the skin; (4) fever is a more prominent feature of epidemic dropsy than of beri-beri, though some Japanese observers insist that there is always some fever in the early stages of beri-beri; (5) infantile epidemic dropsy has been recorded in only a few doubtful cases.

In mild outbreaks the differences between the two diseases may be very slight and may consist only in the greater frequency of loss of the knee-jerks in beri-beri.

Now that argemone poisoning has been established as the cause, examination of the mustard oil used in cooking is the most reliable means of confirming the diagnosis in doubtful cases, although difficulty will arise when the supply of oil used before the onset has been exhausted.

Prognosis. In mild outbreaks there is little risk to life, but sometimes the case-mortality rate may be 50 per cent. or even more. In outbreaks of average severity the death rate is from 10 to 20 per cent. Severe dyspnœa, signs of heart failure, extensive œdema, and a pronounced tendency to hæmorrhages, are the chief signals of danger to life.

Morbid Anatomy. In fatal cases the heart is dilated and usually hypertrophied, especially the right auricle and ventricle. The capillaries are greatly dilated in every part of the body.

Treatment. Complete rest is essential till all symptoms have completely disappeared. Convalescents must lead a very quiet life for months after severe attacks, because of the risk of heart failure.

The use of mustard oil and rice should be forbidden. Those who refuse to accept this advice should get their supplies from a safe source.

The diet is on the same lines as in beri-beri, and so is the general treatment. Thiamin may prove to be of special value in treatment.

Prevention. Attention to the purity of the mustard oil and the condition of the rice supply is the obvious precaution that has to be observed, but often the first indication of danger is the occurrence of swelling of the feet and palpitation in one or more members of the

family or community. Sometimes diarrhœa or dysentery is the first symptom as in beri-beri. In places where the disease is prevalent it is most important to keep a sharp look out for any suspicious symptoms and to change the supply of mustard oil and rice at once.

A diet well supplied with high-grade proteins and all the vitamins is likely to be an additional safeguard.

Famine Œdema

This condition arises through a combination of lack of calories in the diet combined with gross deficiency in proteins. It has been found in concentration and war-prison camps but unfortunately there are many places in the tropics to-day where similar conditions of deprivation exist. The neck and arms of the sufferer are extremely emaciated and pallid but the lower parts of his body, abdomen, scrotum and legs are swollen on account of gravitational œdema. There is *no* protein in the urine which has a low specific gravity. Frequency of micturition and polyuria are common. The protein content of the blood plasma is greatly reduced, especially the albumen fraction.

Treatment. Give an easily digested protein-rich diet so that the *plasma-protein content may improve quickly. Very great care must* be taken not to overfeed to begin with. Glucose and skim-milk powder in warm water may be given in small spoonfuls at short intervals for the first day or two in bad cases. Plasma by the drip method may be given intravenously if available. After a few days the diet may be stepped up and eggs, custards, Marmite-soup, etc., may be added—the object being to get the patient to absorb amino-acids and vitamins to the greatest possible extent.

Kwashiorkor (Chronic Malignant Malnutrition)

Cecily Williams, Trowell and others have described a condition of malignant malnutrition in Africa. The African name Kwashiorkor has been given to it but it is not confined to Africa. Gopalan has recorded an apparently identical condition in South India and similar reports have come from Malaya and the West Indies.

Symptoms. There is great emaciation with anæmia, chronic diarrhœa, crazy-pavement dermatosis, osteoporosis and finally cirrhosis of the liver. Depigmentation of the hair is usual and has inspired the African name. The blood-protein content resembles that in famine œdema, *i.e.*, low total protein content with relatively greater loss of albumen.

Treatment consists of feeding with high-grade proteins (skim-milk preparations are admirable) and in administering *intensive vitamin* B-complex therapy particular stress should be laid on riboflavin and *nicotinic* acid plus specific treatment for helminthic and protozoal parasites when the patient is fit to stand such treatment.

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Infantile Biliary Cirrhosis

This dreaded scourge of better class Hindu infants in India has so far baffled workers attempting to find the cause. Better class Hindu households (often doctors' or lawyers' families) are stricken, infant after infant being snatched away, while poor class Hindus and Muslims in general escape. The disease occurs chiefly in the same class of families in which diabetes is common in adult life. Giving excessive quantities of sweetmeats to the infant has been suspected of being a causative factor, and in any case is a dietetic error. It frequently occurs in infants fed on cow's milk or on combined breast feeding and cow's milk. Cows in Indian cities are always half starved and rarely eat fresh green herbage.

Pathology. A subacute toxic cirrhosis resembling Laennec's cirrhosis. There are signs of patchy regeneration of the liver cells.

Symptoms. The disease attacks children under the age of three—most commonly appearing in the first year of life about the sixth month. The fatal course is run in six to nine months. For some weeks the child is sickly, takes its feeds with no apparent appetite, is slightly feverish and may vomit occasionally. The stools become clay coloured. Palpation of the abdomen reveals a large liver and a palpable spleen. The liver continues to enlarge and deep jaundice gradually develops. Then ascites, œdema of the extremities and finally cholæmia develop. Leucocytosis with relative lymphocytosis is usual.

Treatment. Apart from attending to general principles in giving the mother a vitamin-rich good mixed diet with high-grade proteins during pregnancy little can be done to prevent the onset of the condition. As soon as the diagnosis is made the diet of the child should be changed. A reliable tinned infant milk food should be given with added vitamins and fresh fruit juice. The addition of choline and methionin to the diet is under trial. Large fortunes have been made by the sale of patent "infant liver" nostrums but money is better spent on special diet. A number of recoveries have been reported in cases diagnosed early but the general outlook is gloomy.

DIETETIC DISEASES ASSOCIATED WITH SPECIAL DIETS

Two dietetic diseases deserve special mention ; both have certain features suggestive of pellagra, but are of distinct types and are associated with different articles of diet.

Central Neuritis, or Scott's Palsy, described by H. H. Scott in 1917, is clearly associated with a diet consisting largely of sugar cane ; it occurs as outbreaks among persons harvesting the crop. The onset is sudden with irritative conjunctivitis ; within a few days there is painful inflammation of the mucosæ of the lips and cheeks. After about a fortnight some of the patients have watery diarrhœa which is sometimes fatal, but those who recover have no further symptoms.

DISEASES USUALLY OR INVARIABLY ASSOCIATED WITH CERTAIN FOODSTUFFS

Disease	Beri-beri.	Epidemic dropsy.	Pellagra.	Scott's disease.	Moore's disease.	Lathyrism.	Favism.
Food	Rice.	Argemone oil and rice.	Maize.	Sugar-cane.	Manioc.	*Vicia sativa.*	*Vicia fava.*
Chief features	Gastro-intestinal disorders; neuritis; œdema; cardiac disorders.	Œdema; cardiac disorders; gastro-intestinal disorders.	Gastro-intestinal disorders; dermatitis; glossitis; mental symptoms.	Conjunctivitis; stomatitis; gastro-intestinal disorders; neuritis.	Glossitis; dermatitis; optic neuritis.	Neuritis; spastic paraplegia.	Gastro-intestinal disorders; anæmia.
Probable causative factors.	Vitamin deficiency *and intoxication.*	Intoxication.	Vitamin deficiency and intoxication.	Intoxication.	Vitamin deficiency and intoxication.	Intoxication.	Intoxication.
Chief curative vitamins.	Vitamin B_1.	Not known.	Nicotinic acid.	Not known.	Vitamin B-complex.	Not known.	Not known.

The other patients are constipated and some of them suffer from numbness and tingling of the feet, progressive weakness, and loss of the knee-jerks. Some of these patients die.

Scott appears to have been justified in regarding the disease as a dietetic intoxication.

A pellagra-like disease was described by D. F. Moore in 1934 as occurring specially among school children in Nigeria who lived largely on the tubers of the cassava plant which is also called manihot or manioc. Clarke (1941) regarded the disease as a form of pellagra and suspected it of being caused by a toxic glucoside contained in cassava. The chief symptoms are soreness of the tongue, angular stomatitis, scaly and itchy dermatitis, and dimness of vision caused by retrobulbar neuritis.

Moore (1943) states that nicotinic acid has no curative action; riboflavin causes some improvement, but Marmite is needed for complete cure. Manihot has been found by Chick to be deficient in riboflavin, but Moore insists on the importance of giving an adequate supply of "protective" foods in all cases in which "dead" foods such as rice, sago, tapioca, arrowroot, etc., are being eaten as the staple articles of diet. This advice is sound and should be followed in all dietetic diseases whether they are regarded as being caused solely by dietetic deficiencies or are considered to be due to toxic factors of dietetic origin.

These two diseases described by Scott and Moore show a striking analogy with beri-beri and pellagra in being specially associated with particular articles of diet. The table shows some of the chief features of certain diseases that are known to be specially associated with particular foods; it has been prepared for the purpose of emphasising the importance of the kind of food that is eaten as well as the vitamin content of the diet.

Medical men in the tropics encounter many cases of dietetic diseases which do not show the clinical features of any of the recognised clinical syndromes and therefore have to be classified under the heading of miscellaneous dietetic diseases. In all cases in which one or more of the following signs and symptoms cannot be fully explained on other grounds the diet should be investigated from the points of view of general inadequacies, deficiencies and intoxications. These are: weakness; various types of neuritis; œdema; gastro-intestinal disturbances; cardiac disorders; anæmia; soreness of the mouth, lips or tongue; dryness and scaliness of the skin; conjunctival irritation; vascularisation of the cornea; follicular conjunctivitis; night-blindness; and mental enfeeblement.

In such cases treatment by a generous ideal diet combined with the withdrawal of any article which is suspected of being associated with the disease will usually give gratifying results. Treatment by single vitamins will often be unsuccessful.

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Chief curative vitamins.	Vitamin B_1.	Not known.	Nicotinic acid.	Not known.	Vitamin B-complex.	Not known.	Not known.

lesions in the dorsal region. These are probably caused by a prolonged condition of spasm of the arteries supplying the cord.

Symptoms. The disease varies greatly in severity. The mildest forms of the disease are often missed.

In an outbreak observed by Megaw in a Calcutta jail in 1911, the commonest early symptoms were burning pains in the feet and legs, weakness and wasting of the muscles. Gradually the gait became stiff and cramped, and the knee-jerks much exaggerated ; dimness of vision was common. Constipation was usual, but in some cases there was irregular diarrhoea. The disease ran a chronic course with periods of exacerbation and remission. After exclusion of *dal* from the diet the disease soon disappeared.

In the more severe forms the disease may begin gradually with the symptoms already described, or may come on rather rapidly. The condition becomes one of spastic paraplegia or paresis. In mild cases the patient has a stiff gait, but is able to walk without aid or with the help of a stick. In the more severe forms he requires crutches, or is bed-ridden.

There is usually exaggeration of the knee-jerks and ankle clonus. Impotence and incontinence of urine are frequent and troublesome symptoms in severe cases. Occasionally there is loss of control of the bowel, but severe cystitis is not common, so that there is little danger to life.

S. R. A. Shah has described an outbreak affecting sixty-four persons in a community of 205 within a period of a few months. In thirty-four there were gastro-intestinal symptoms followed by tingling of the soles, numbness and formication ; still later there was spastic diplegia which gradually became flaccid. The onset was sudden in thirty cases.

Great improvement or cure can only be expected when the disease comes under treatment in the early stages.

Diagnosis. The slighter forms of lathyrism are rarely recognised, being usually mistaken for irritative neuritis of obscure origin. If suspicion is aroused, an inquiry into the diet will usually enable the physician to detect the cause and control the outbreak.

In early cases the response to a suitable diet will clear up the diagnosis.

If the suspected *dal* is available it should be given to experimental monkeys or rabbits for several weeks to find out whether it is toxic. Samples should also be sent to a botanist for identification. The after-effects of the severe forms of lathyrism closely simulate syphilitic paraplegia, but an inquiry into the history of the patients will usually elicit evidence pointing to the nature of the disease. When several cases occur at the same time in a community which uses *dal* as an article of diet the diagnosis will be clear. In doubtful single cases a positive Wassermann reaction suggests syphilis, but it must be remembered that the reaction is positive in 10–15 per cent. of the

DISEASES CAUSED BY FOOD INTOXICATION

Lathyrism

The name is derived from the word *lathyrus*, which is the name of leguminous plants of the chick-pea type.

Lathyrism, like beri-beri and pellagra, is closely associated with the use of a special article of diet. Eating the seeds of *Vicia sativa* is the chief cause of lathyrism, but the seeds of other closely related vetches, especially *Lathyrus sativus*, are also suspected of being responsible in some cases.

Definition. *Lathyrism is a food intoxication caused by eating the seeds of Vicia sativa or other related vetches.*

Distribution. Far more cases occur *in India than in the whole of* the rest of the world. The disease in India has a restricted distribution, being confined for the most part to the central plateau, North Behar, and some districts in the United Provinces (*see* Fig. 84).

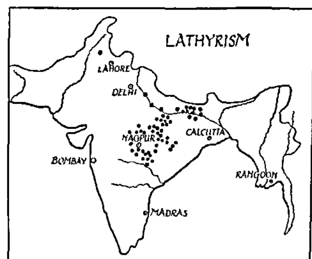


Fig. 84. Map of distribution of lathyrism in India.

The disease also occurs, though less frequently, in France, Italy, and Algeria.

Horses, elephants, cattle, sheep, monkeys, and other animals, are liable to be attacked if *they eat the grain that* causes the disease. The seeds of *Vicia sativa* are not usually eaten by those who can afford safer and better articles of food, hence the disease is specially common among poor people and in times of famine. Young male adults are the chief victims.

Ætiology. The disease was formerly believed to be caused by eating the seeds of *Lathyrus sativus*, which is often called "khasari dal" in India, but Howard, Anderson and Simonsen failed to find any poisonous substances in *Lathyrus sativus*, whereas they isolated a toxic alkaloid, "vicine," from *Vicia sativa*, another kind of vetch whose seeds are frequently present as an adulteration in samples of "khasari dal." *Vicia sativa* is commonly known as *akta* in India; its seeds have been found capable of causing symptoms of lathyrism in ducks and monkeys. Apparently the poison is normally present in the seeds, but there is still a good deal to be learned about the conditions in which the toxic agent is most abundant in the grain.

The pathological changes in the spinal cord consist of sclerotic

CHAPTER XXV

CLIMATE AS A DISEASE FACTOR

ALTHOUGH everyone knows in a general way what climate is, the meteorological experts have failed to give a simple and satisfactory defintion of the word. Such defintions as " the average conditions of the atmosphere " or " the average weather " are not very helpful even with the additional information that the word weather denotes a single occurrence or event in the series of conditions which make up climate and that these conditions consist chiefly of the temperature, humidity and movement of the air, the rainfall and the sunlight. The climate of a place cannot be described accurately in terms of the yearly average of each of these conditions because the same average, especially in the case of temperature, may be recorded in places with great daily and seasonal variations and in places with uniform conditions throughout the year.

With so many variable factors it is impossible to give a simple classification of the climates of the world.

In the tropical climatic zone, with which we are specially concerned, weather conditions are relatively uniform in places at low levels. This zone can be regarded as being bounded on the north and south by the annual isothermal lines of 68° F. ; it is wider than the geographical torrid zone and includes nearly all of South America, Mexico and Africa, most of South Asia and more than half of Australia. In most of these land areas the weather is hot and moist throughout the year, but at high levels it can be cool or cold and in inland areas far removed from the moderating influence of sea breezes there may be great daily and seasonal variations in the temperature, especially near the margins of the zone. It appears, therefore, that even in the tropics there are many different kinds of climate and that the term " tropical climate " is not necessarily the same as " the climate of the torrid zone."

CLIMATE AND HEALTH

Climatic conditions affect the health of human beings in several ways :—

(*a*) Directly. The conditions of temperature, moisture and movement of the air, taken together, may be favourable to the vitality and energy of the body, they may act unfavourably by lowering resistance to disease, or they may actually cause diseases like heat-fever or frost-bite.

Light may act in a favourable or unfavourable manner ; excess of light gives rise to solar dermatitis and night-blindness ; defect of light is one of the causes of rickets and osteomalacia. Light may increase vitality when it falls on the body in suitable amounts, whereas either deficient or excessive exposure to light causes a lowering of vitality.

population in most of the places where lathyrism occurs, so that the test is not entirely reliable as a means of excluding lathyrism.

Treatment and Prevention. *Dal* should be excluded from the diet: if this is impracticable the *dal* which has been in use should be rejected and replaced by a kind that is known to be wholesome.

The reason for advising the complete exclusion of *dal* is that the toxin appears to have a cumulative effect, so that wholesome *dal* may contain enough poison to be harmful to persons already affected by the disease. For this reason all kinds of *dal*, even those that are harmless to healthy persons, should be prohibited to patients suffering from lathyrism. The diet should be nutritious and generous; high-grade proteins and vitamins are specially important. Treatment of the spastic paraplegia or paresis by massage, postural measures, etc., may be helpful in recent cases, but long-established paraplegia is incurable.

Favism

In certain Mediterranean countries a severe intoxication occurs in persons who eat a special type of broad bean (*Vicia fava*) in the uncooked condition.

The onset is sudden, with vomiting followed by diarrhœa. Anæmia of the hæmolytic type rapidly develops, but usually there is speedy recovery.

Ackee Poisoning

In the West Indies and the West Coast of Africa a severe and often fatal poisoning results from eating the unripe fruit called ackee. The ripe fruit is harmless.

The symptoms are vomiting within one to three hours after eating the fruit followed by abdominal discomfort lasting three or four hours. There may be no further symptoms, but in most cases, after a brief period of freedom from discomfort, severe vomiting, convulsions, and coma, occur; these are said to be invariably fatal.

Alcohol precipitates the poison; Scott found that the immediate administration of rum and ammonia reduced the fatality rate from 90 to 27 per cent.

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G. R. McROBERT

acclimatised to heat is to expose the body as much as possible to the highest temperatures that can be endured. It is true that the human frame does gradually adapt itself to such climatic conditions as heat, cold and the rarefied air of high altitudes, but there are strict limits to the degree of acclimatisation that can be acquired; when these limits are exceeded the resisting powers of the body rapidly *diminish*. So it is that newcomers to the tropics, in spite of their lack of experience, can often endure spells of great heat better than those who have become enfeebled by prolonged exposure to hot weather.

The best way to keep fit in hot climates is to take every opportunity of getting cool and keeping cool; by doing this the ability to tolerate spells of heat will be improved and at the same time the power of reacting to cold will be retained.

SUNLIGHT

The chief properties of the rays of the sun are shown in the table. The classification is not strictly accurate; for example, some of the chemical rays are also luminous, though to a limited degree; the luminous rays also have a slight heating effect.

Sunlight in the tropics is usually much more intense than in cold climates, but in other respects it has no mysterious properties. Special protection is needed only because of the greater activity of the heating, luminous and chemical rays. Precautions against the tropical sun are

PROPERTIES OF THE RAYS OF THE SUN

	Visibility	Chief Actions	Diseases Caused
Heat rays.			
1. Infra-red.	Invisible.	Heating.	Heat-exhaustion. Heat-fever.
2. Red.	Visible.		
Luminous rays.			
3. Orange. 4. Yellow. 5. Green.	*Visible.*	*Chiefly illuminating.*	Glare-headache. *Night-blindness.*
Chemical rays.			
6. Blue. 7. Indigo. 8. Violet.	Visible.	Stimulating and anti-rachitic in moderate doses. Irritant and destructive of tissues in excessive doses.	Solar dermatitis. Pigmentation.
9. Ultra-violet.	Invisible.		

often carried to absurd extremes; many Europeans shut themselves up in darkened rooms throughout the day and so suffer from deprivation of the health-giving properties of sunlight.

During spells of extreme heat the sun ought to be avoided as much as possible; otherwise a moderate degree of exposure to the sun, especially in the cool of the morning, is desirable.

(*b*) Indirectly. The crops of a place, and hence the food supply of the people, depend largely on climate.

Insect life is greatly influenced by climate. Insect-borne diseases *can only be transmitted when climatic* conditions are suitable for the existence of the vectors, for their ability to bite, and for the development of the parasites in their bodies.

The influence of climatic conditions on the transmission from man to man of droplet, dust-borne, alimentary and even direct-contact infections is well recognised and is a subject deserving further study in view of its importance to public health workers. L. Rogers has shown that epidemics of cholera in India can be predicted with a considerable degree of accuracy by observations of meteorological conditions, and the same thing has been done in connection with malaria by C. A. Gill in the Punjab.

General Effects of Tropical Climates on the Human Body

The depressing and enervating effect of tropical heat on the human body is a matter of common knowledge ; the explanation in simple terms is that in hot atmospheric conditions there is a diminution of the activity of the heat-producing tissues which need the stimulating effect of a cool environment if they are to be kept in a high state of efficiency. The feeling of lassitude which is normal in tropical weather is in itself a protective reaction to conditions in which energetic physical work is likely to have harmful effects.

There is no need, however, to adopt a fatalistic attitude towards conditions of life in the tropics ; although it is not possible to change the climate much can be done to promote better standards of health and comfort by adopting habits suited to the state of the weather and by making an intelligent effort to provide a cooler environment in the houses in which a large part of each day is spent. If people took as much trouble to keep cool in the tropics as they do to keep warm in cold climates they could avoid most of the adverse effects directly due to atmospheric heat.

Certain prejudices must be overcome ; one of these is the exaggerated fear of chill ; this probably has its origin in the fact that most fevers begin with a chill which has come to be regarded as the cause of the disease instead of a symptom. Owing to this prejudice many people *try to avoid the slightest feeling of cold or even coolness* of the skin instead of welcoming it as a sign that the body is reacting in a healthy way to the tonic action of cool air. Persons who coddle themselves gradually lose this power of reacting to cold and so become very liable to suffer from damage *when they are exposed to real cold.*

Local chilling, especially of the abdomen, is dangerous even for those who have retained the power of reacting to cold ; the aim should be to cultivate a feeling of coolness of the whole body.

Another mistaken belief is that the best way of becoming

because a good *topi* protects the head and part of the body from the heat-rays of the sun, and so helps to ward off heat effects.

Corrie in Senegal has made some interesting observations on the air temperature inside various kinds of head-dress in noon-day tropical conditions. The records were

(1) *Pith helmet, with white cover and ventilation* 35·6° C.
(2) French sailor's cap, with white cover . . 40·0° C.
(3) French sailor's cap, without cover . . 41·0° C.

A large thick pith *topi* with effective ventilation round the rim and in the top is the best form of protection for the head.

An umbrella is even better than a *topi*, it protects a much larger area of the body from the heat rays of the sun. When the sun is low in the sky any kind of head-dress can be worn with safety.

HOUSES IN THE TROPICS

Many modern houses in the tropics are far less comfortable than the old thatched bungalows with their thick walls and wide verandahs. The climatic conditions of different places in the tropics are so varied that no single type of construction is suitable for all hot countries. A few general principles applicable to places with a season of intense dry heat and to those in which there is moist heat without excessively high temperatures are as follows.

(1) *In places with intense dry heat the rooms should be lofty* and fitted with doors and windows which can be closed so as to keep out hot air and sunlight in the heat of the day. Clerestory windows of a good size are essential. The roof should be insulated, preferably by being double, with a free ventilation space between the two layers. The walls, if possible, should also be double with a ventilation space in the middle: if this is impracticable the walls should be thick, and should be shaded from the sun by wide verandahs. All the outside surfaces of the house should be white.

Single-storied bungalows with the lowest possible plinths have the great advantage of covering a large floor area which remains cool for a *considerable time after the onset of the hot weather*. The reservoir of coolness which is provided by the earth under the house is not sufficiently appreciated; its effectiveness can be greatly increased by having a well-watered lawn round the building.

If a double roof cannot be provided the single-storey type of building is less suitable because the air inside the rooms gets heated by radiation and convection from the hot roof: in a two-storied building the ground-floor rooms are well protected against this source of heat, and the upstairs rooms, though hotter by day, are likely to be cooler and more airy at night than the lower part of the house.

In very hot weather the house should be completely closed up as soon as the outside air becomes hotter than the inside; in the evening,

CLOTHING IN THE TROPICS

It would be easy to devise suitable clothing for tropical wear if custom did not impose rigid restrictions on our choice. There are many places in which complete nudism combined with the use of a large umbrella would be ideal at certain times of the year. In the strict privacy of one's room the less clothing is worn the better during very hot weather.

For everyday wear the clothing ought to be white in colour, thin in texture, and loosely fitting.

A tennis shirt, open at the neck, and shorts are often the most suitable costume. Shorts are usually worn with a belt, but this method of support has the drawback of constricting the waist and preventing the free circulation of air over the surface of the body so that the cooling effect of evaporation of sweat is diminished ; a better plan is to attach the shorts to buttons sewn on a band fastened permanently on the shirt.

Long trousers have decided advantages on many occasions ; they protect the legs from the heating effects of the sun, from the bites of insects and snakes, and from mechanical injury when walking through scrub or undergrowth : if they are attached to the shirt as suggested above they are cooler than shorts when the sun is strong.

White clothing gives the best protection against the heat rays of the sun; next best is pale blue or a light khaki tint ; black is the worst of all in this respect.

There is no need for special fabrics designed to keep out the ultra-violet rays ; the thinnest white material prevents the penetration of all but a very small percentage of these rays.

In hot weather the only part of the body that needs protection at night is the trunk ; a light woollen blanket or shawl should be wrapped round the abdomen and chest to prevent local chilling of these parts by the sudden and unexpected drops in the temperature that are liable to occur during the night. Attacks of diarrhœa often result from chilling of the abdomen, especially in persons who have suffered from dysentery.

After exercise a tepid bath should be taken, followed by a change into light flannel clothing. The habit of putting on a sweater or greatcoat over sodden clothing is insanitary, it reproduces the conditions of a Turkish bath and prevents the over-heated body from cooling down.

Women's clothing should conform to the same general principles as have been laid down already, it should be white, light and loose ; it should also protect the body from insect bites.

Head-Wear

This is of great importance, not because it is necessary to take elaborate precautions against any mysterious "death rays," but

The "thermantidote" works on the same principle, but a hand-operated fan is used to propel the air through the screen.

A modern development of the thermantidote was devised and used by myself about thirty years ago ; this consisted of a large box fitted into a doorway ; the outer side was replaced by a *khus-khus* screen kept wet by a drip from an overhead tank ; on the inner side there was a circular opening into which was fitted an electric fan by which the air from outside was sucked through the meshes of the wet screen and discharged into the room Even with outside shade temperatures of 115° F. the air of the room was remarkably cool ; the running costs were low.

There is great scope for the development of systems of air cooling based on the evaporation of moisture ; the following are suggested as examples :—

(1) In places with seasons of intense dry heat, hospitals, barracks, etc., could be specially constructed for ventilation and air-cooling by the device described above ; at the opposite end of each room an exhaust fan can be fitted so as to provide a steady flow of cool, fresh air from one end of the room to the other. The system would work best in long, low, and rather narrow rooms so that the initial cost of the building would be considerably reduced. Ventilation would be perfect, the room would be cool, free from dust, and insect-proof. Better lighting could also be provided than is possible in ordinary rooms in the heat of the day.

(2) Railway saloons could be kept cool by fitting a *khus-khus* screen *in the front of each carriage ; this would be kept moist by a drip from* a tank under the roof, and the rapid movement of the train would create a flow of air through the screen.

A similar device could easily be fitted to a motor car at a trifling cost.

(3) Invalids can be safely conveyed by train in the hottest weather by the use of a simple device. A frame shaped like a surgical cradle is placed over the patient. The frame is covered by a large sheet of thick towelling material which is adjusted so as to leave only the head of the patient exposed. If the sheet is kept wet and the breeze from an electric fan allowed to play on it the air inside will be remarkably cool ; in fact care must be taken to avoid chill.

It should be noted that all devices for cooling air by the evaporation of moisture will be effective only when *dry* air passes over the moist screen. Some people have made the elementary mistake of fixing up the contrivances inside a room so that the same air is used over and over again. The results have naturally been most disappointing ; the air of the room soon becomes saturated with moisture and the cooling effect is abolished.

This objection does not apply to the third example given above because the air inside most railway carriages is being constantly changed when the train is moving, and so remains dry.

when these conditions are reversed, every door and window should be opened wide. Special attention must be paid to the opening up of the clerestory windows at night, it is through them that the heated air escapes most rapidly.

At least one or two of the rooms should be constructed in such a way as to make them suitable for the installation of an air-cooling or air-conditioning apparatus (*see* p. 498).

(2) In places where the air is moist and the temperature never rises to great heights, *the chief aim should be to provide for the freest* possible degree of through-ventilation.

Insulation of the roof is not so important in places where moist heat prevails as in those with intense dry heat, because the rooms are usually kept open all day so that the upper layers of air which are heated by contact with the roof are constantly swept away by the through breeze and the temperature of the air in the lower part of the room is only slightly raised. There is, however, a certain amount of heating of the room by radiation from the hot roof and walls so that insulation of these is desirable even when through-ventilation is adopted.

It will be seen that the problem is by *no means simple*; more research and experiment are needed before comprehensive rules can be laid down for the construction of buildings suitable for the varied conditions which exist in the tropics.

Such matters as the cost and availability of building materials, the orientation of the building, the choice of a suitable site, the mosquito-proofing of the house, etc., must also be considered.

Every locality has its own special problems, so that there can be no question of proposing standard types of building suitable for all places in the tropics.

AIR COOLING IN THE TROPICS

For hundreds of years efforts have been made to escape from the fierce heat that prevails in some tropical countries.

Underground rooms have long been used in certain countries in which a season of great heat alternates with one of cold weather. In these rooms the air is kept cool by the surrounding earth which has become cooled during the winter and remains relatively cold during the greater part of the hot season.

Other methods are based on the cooling effect produced by the evaporation of moisture. This simple and cheap *method of air cooling* has been strangely neglected, it is very effective in places where intense dry heat prevails.

The old-fashioned **khus-khus tattie** consists of a thick screen woven from a special fibre, this is placed in a doorway facing the prevailing wind and is kept moist; the air which passes through the wet screen is cooled to a remarkable degree.

tion in the red cell-count and in the hæmoglobin percentage occurs. A condition known as stoker's anæmia was long regarded as an occupational disease caused by a diminution in the production of red blood cells, but little has been heard of this disease in recent times and it can be regarded as doubtful whether a hot environment by itself causes anæmia though it may be a predisposing factor in the causation of anæmia.

II. Tropical Liver

The names "tropical liver" and "tropical congestion of the liver" are often given to a clinical syndrome which is common in hot climates, especially among immigrants from cold countries.

The chief features of the condition are: headache, lassitude, loss of appetite, furring of the tongue and a feeling of heaviness or discomfort in the region of the liver; in severe cases there are also enlargement and tenderness of the liver and the face has an earthy or subicteric tint.

Tropical climate by itself does not cause the illness, though it lowers the resistance of the liver to damage by the real causative agents which include various latent infections such as malaria and amœbiasis, nutritional disorders resulting from dietetic errors and excesses, over indulgence in alcohol and lack of exercise.

The physician should never be satisfied with the diagnosis of "tropical liver," which suggests that the liver is to blame for its failure to withstand the effects of heat, whereas it is the innocent victim of damage done by infection, intoxication or undue stresses imposed on the organ by faulty habits of life; these are the causes to which attention must be directed.

III. Tropical Neurasthenia

Definition. The clinical features of neurasthenia are much the same in the tropics as in other parts of the world so that the only justification for retaining the name tropical neurasthenia is that in hot countries the adverse climatic and other conditions of life peculiar to the tropics are the chief causative factors of the disease. Neurasthenia itself is a disorder whose causes and symptoms are so many and so varied that it cannot be defined in concise and universally acceptable terms; it may tentatively be described as a form of neurosis whose chief features are irritable nervous depression and anxiety with loss of self-confidence and capacity for sustained mental effort.

Although anxiety and depression are features of neurasthenia the patients fully retain a sense of responsibility and intelligent awareness of the disorder, which must therefore be distinguished from the psychoses called anxiety and depressive states; the term psychosis should be strictly avoided in connection with true neurasthenia.

Pathology. The signs and symptoms supply the only tangible

MODERN METHODS OF AIR COOLING

Modern methods of refrigeration have opened up great possibilities of cooling the air of living-rooms, but although cold rooms have long been used for storage and other industrial purposes there was a strange reluctance to adopt refrigeration for cooling the air of rooms occupied by human beings.

The first plant of this kind, at any rate in the tropics, was initiated by me in 1913 when the late Mr. Willcox, a refrigeration expert, designed and installed an air-cooling system in a laboratory at the Calcutta School of Tropical Medicine. Owing to the war of 1914–18, this was not taken into use till 1920 ; since that year it has worked quite successfully. The room reproduces the conditions that prevail *in a well-ventilated laboratory* in a temperate climate.

At first the scheme evoked a great deal of criticism, but it was soon found that fears of danger to health were groundless ; in fact the health and working capacity of the occupants have been much improved.

Installations of a similar type were gradually adopted in hospitals, operating rooms, and offices, in India.

The greatest development of air-cooling has taken place in the U.S.A. where elaborate " air-conditioning " plants have been introduced on a large scale for trains, motor coaches, and buildings of many kinds. By this system provision is made for heating the air in cold weather as well as for cooling it in hot weather, and the air moisture is kept constant. These plants are now used in many places in the tropics.

Air-conditioning units suitable for small rooms or cubicles are now *available ; they are likely to become necessities of life in* tropical countries for all who can afford them. Their initial and running costs are relatively small and they are equally suitable for places with moist and dry heat. There is, however, still great scope for the development of the cheaper devices based on cooling by the evaporation of moisture.

DISEASES CAUSED BY HIGH AIR TEMPERATURES

The general diseases caused directly by hot climatic conditions will be described under the heading of " Heat Effects " but a brief reference must be made to two morbid states of doubtful standing which have traditionally been regarded as being caused by tropical climate. These are " tropical anæmia " and " tropical liver." Another disease, tropical neurasthenia can suitably be described as being associated with hot climates for reasons which will be given later.

I. Tropical Anæmia

An increase in the total volume of the blood has been observed among persons who have recently gone to the tropics so that a diminu-

way, and equal interest must be taken in the history of previous illnesses.

The patient is usually highly sensitive and often is highly intelligent: he must be handled accordingly if a proper understanding is to be established between him and yourself.

After a thorough investigation the next step is to give the patient a frank and truthful statement of the nature and causes of his illness. This is a delicate matter which makes great demands on the tact of the physician. The words neurasthenia and nerves usually convey a wrong impression to the patient: a term like "brain-fag" is far more likely to be understood, especially if the patient can be convinced that this is the natural result of the unfavourable conditions in which his brain has been working and is no more mysterious than a state of physical exhaustion due to overwork of the muscles.

The necessity for removing the causes of the trouble must be emphasised; in serious cases the need of prolonged rest in favourable surroundings is pointed out, but a confident assurance of complete recovery can usually be given. In most cases it will be necessary to persuade the patient that he must acquire a more reasonable outlook on life; he is usually a hard-working and over-conscientious person who must be made to realise that overwork, especially if combined with worry, can only result in bad work.

Temperamental defects are not easy to overcome, but an intelligent patient will usually co-operate in the cultivation of equanimity and a sense of proportion when the need for these is explained.

In cases of doubt a neurologist rather than a psychiatrist should be consulted unless there is definite evidence that the patient's illness is a psychosis for which restraint may be needed. Differentiation from the early stage of a progressive nerve disease like disseminated sclerosis may sometimes be difficult, and even expert neurologists have been known to diagnose an incurable nervous disease in cases of neurasthenia.

Prognosis. The prospect of complete recovery is good when it is possible to eliminate the causes and to provide for an adequate period of convalescence in pleasant and healthy surroundings. The question of fitness to return to the tropics after recovery has to be decided according to the circumstances of each case; it will often be easy to predict that a relapse will occur if a more favourable environment cannot be provided and in many cases it is obvious that the patient should never have been allowed to take up work in the tropics to begin with. On the other hand if the disorder has occurred in specially unfavourable conditions which are unlikely to recur and recovery has been complete a second chance can justifiably be given.

HEAT EFFECTS

The clinical effects resulting from exposure to excessive heat are extremely varied in character and intensity; they can most con-

evidence of the morbid changes which must be assumed to occur in the nervous system, especially in the higher centres of the brain which are concerned with such mental functions as thought, memory and imagination.

Symptomatology. The patient feels tired, depressed and irritable; there is a distressing consciousness, of inability to concentrate on mental work, of emotionalism, and often of defective memory. *Insomnia is usual*; *giddiness* and a feeling of pressure on the head are often complained of. An element of hypochondria or hysteria can often be observed. There are few physical signs apart from increase of the deep reflexes and muscular tremors. The blood pressure tends to be low.

Causes. Examples of the chief causative factors are as follows :—

(1) *Cosmopolitan causes* such as inherited instability of the nervous system, an unhealthy outlook on life acquired by unfavourable environment in the family and school in early life, worry, overwork, sexual factors, alcohol, the effects of other diseases, head injuries, etc.

(2) *Adverse Conditions associated with Life in the Tropics.* (*a*) Prolonged exposure to heat, especially in places where the climate is trying all the year round.

(*b*) Other unfavourable environmental factors such as uncongenial conditions of work and social life, unsuitable diet, too much or too little exercise.

(*c*) Existing or preceding tropical diseases like malaria, dysentery, amœbiasis, dengue and heat fever.

Diagnosis. The diagnosis is usually obvious even before the patient has finished the story of his complaints, but there can be no greater mistake than to tell the patient bluntly that he is suffering from "nerves" or even neurasthenia. A hasty diagnosis of this kind conveys to the patient a completely false impression of the nature of his disease; it suggests to him that the doctor regards the illness as imaginary, whereas he is painfully conscious of suffering from a real disability. Some patients are antagonised, others feel that the doctor has failed to understand the case. Whichever of these unfortunate impressions is conveyed there will be a fatal lack of confidence on the part of the patient.

Doctors have been known to make matters worse by telling the patient to pull himself together and to refuse to let his nerves get the better of him.

Treatment. The first essentials to success in handling cases of neurasthenia are to make a complete physical examination and to avoid conveying the impression to the patient that he is to blame for his illness or that his disease is of a mysterious kind.

Although it is essential to obtain a full history of all the domestic, social and occupational factors that may have a bearing on the case the questions dealing with these should be asked in a matter-of-fact

heating of the body by the air ; in such conditions the heat-regulating mechanism obviously has to make a great effort to keep the temperature of the body from rising above the normal upper limit.

J. S. Haldane's experiments are of great importance in showing the degrees of atmospheric heat and moisture which can be tolerated by the healthy human body ; if these are exceeded the body temperature begins to rise and continues to go up in an inexorable manner, so that heat-fever would certainly result if the unfavourable conditions were allowed to continue too long.

Haldane found that the body temperature began to rise in persons subjected to the following conditions : –

(1) At rest in still air – wet-bulb temperature . 88° F. or over.
(2) .. .. .. moving air – .. .. . . 93° F. ,,
(3) Doing moderate work in still air – wet-bulb temperature . . . . . . 78° F. ,,
(4) Doing moderate work in moving air – wet-bulb temperature . . . . . . 86° F. ,,

He found that the rise of temperature became more rapid the higher the wet-bulb temperature ; for instance, the person at rest in still air showed a rise at the rate of 1° F. every hour when the wet-bulb temperature was between 89° and 90° F., while the rise was 2° F. every hour when the wet-bulb temperature was 94° F.

Haldane's experiments show – (1) the influence of air moisture (it is the wet-bulb temperature that counts ; the height of the dry-bulb thermometer does not matter much until very high temperatures are reached) ; (2) the influence of work ; and (3) the very helpful effect of air movement.

The influence of work is also shown by the fact that a soldier at rest produces 1·2 calories of heat every minute ; the same man while marching with a load of 65 lb. produces nearly 8 calories a minute, which would raise the body temperature 1° C. in nine minutes if no heat-loss were occurring.

In ordinary conditions in the tropics a wet-bulb temperature over 83° F. is regarded as involving special risk.

C. J. Martin found that the naked human body when exposed to a very hot sun absorbed three times as much heat as is produced by the body while at rest. This shows the importance of the part played by the direct rays of the sun in causing heat-fever.

Actual observation of the conditions in which heat-fever occurs shows that the disease affects human beings exactly as would be expected from the foregoing experimental data.

L. Rogers analysed the fatal cases recorded in India during several years.

The monthly incidence was found to be : January to April, 0 ; May, 7 ; June, 31 ; July, 15 ; August, 4 ; September, 3 ; October-December, 0.

veniently be described under the following headings :—(1) heat-fever or heat-hyperpyrexia ; (2) heat exhaustion of two types : (a) hidrotic ; (b) anhidrotic ; and (3) heat-cramp.

This classification is based on the most prominent clinical feature of each type.

I. Heat-Fever

Synonyms. Heat-stroke, heat-hyperpyrexia.

Definition. This is the type of heat-effect characterised by a progressively rising temperature which if not checked becomes hyperpyrexia.

The name heat-fever is more suitable than heat-stroke or heat-hyperpyrexia which cannot rightly be applied to the early stage of the condition. The name sun-stroke should not be used ; the disease can occur in complete darkness. The heat rays of the sun often play an important part in causing heat-fever, but they have no mysterious action ; they simply heat the body and thus add to the adverse effects of high atmospheric temperatures. Heat-fever occurring in persons who have been exposed to the rays of the sun is the same as the disease caused by heat in a darkened room. The disease is by no means confined to the tropics ; in cities like New York and Chicago there are as many cases of heat-fever as in Singapore or Calcutta, yet heat is the essential cause of the disease ; cases never occur unless the atmospheric conditions are such as to put a heavy strain on the heat-regulating mechanism of the body.

General Considerations

The living body is constantly producing heat ; if there were no loss of this heat the temperature would continue to rise to a fatal degree.

In normal conditions heat-production and heat-loss balance each other in such a way that the temperature of the body keeps within narrow limits irrespective of the temperature of the air or the rate of heat-production by the body. This balance is maintained by the heat-regulating mechanism, which is controlled by the heat-regulating centre.

In cold weather heat-loss takes place chiefly by radiation and convection of heat from the surface of the body ; for example, C. J. Martin found that a person wearing ordinary clothing in a room at a temperature of 15° C. and with a relative air humidity of 50 per cent. lost nearly half of the excess heat by radiation, 31 per cent. by convection and 20 per cent. by evaporation of moisture from the lungs and skin. In warm weather evaporation plays a much larger part and in very hot weather when the air temperature is higher than the body temperature, heat is actually taken up from the air by the body, so that evaporation has to take on the double task of getting rid of the excess heat resulting from heat-production together with that due to

or other fevers are exceptionally liable to heat-fever. Persons under an anæsthetic or recovering from an operation are also very susceptible.)

Condition of the sweat glands. (Numerous and active sweat glands help in lowering the body temperature)

Race. The dark-skinned races are less susceptible in spite of the fact that pigmented skin absorbs more heat from hot air than white skin. Factors which may help to account for the lower susceptibility of pigmented races are :

(*a*) Diet of low calorie value, (*b*) More suitable clothing; (*c*) Abstinence from alcohol, (*d*) Avoidance of over-exertion; (*e*) Experience : (*f*) Lowered metabolic activity ; (*g*) Slender build (the surface of the body is relatively large in persons of light weight as compared with those who are heavy, and therefore heat-loss by the evaporation of moisture from the skin is more effective in the case of persons of slender build)

Sex. Females rarely suffer, they are less often exposed to the conditions which conduce to the disease, and the metabolic activity of their bodies is lower than that of men.

Exposure to the Sun. The direct heating effect of the rays is the important factor. Only 1 per cent. of the ultra-violet rays can penetrate to a depth of 1·5 mm. into the skin, so that damage cannot be done to the brain and spinal cord by these rays.

Liquid Intake. C. J. Martin found that in trying atmospheric conditions, evaporation of a pint of liquid from the body every hour was needed to maintain a constant temperature during hard work. Hence the importance of a good supply of drinking water.

Salt-intake. Much sodium chloride is excreted with the sweat ; a sufficient ration of common salt is important.

Weight. Persons of heavy build are more susceptible than those who are slender, for the reason already given.

Age. The disease is more frequent after the age of thirty.

Duration of Residence in the Tropics. The incidence of heat-stroke in British soldiers according to duration of service in India was as follows :—

First 2 years, 1·5 cases per mille.
3rd and 4th years, 0·65 cases per mille.
6th to 8th ,, 0·75 ,, ,,
11th ,, 14th ,, 1·62 ,, ,,
15th and later years, 3·50 cases per mille.

Experience and acclimatisation evidently tell at first, but later on their influence is more than neutralised by the unfavourable influence of age and of lowered vitality due to long residence in the tropics.

Overcrowding and bad ventilation are very important factors. In a closed room occupied by human beings the humidity of the air rises rapidly ; increase of air moisture combined with absence of air movement are very conducive to heat-stroke when the temperature is high.

In each locality three-fourths of the fatal cases occurred during the hottest month of the year.

The mean daily air temperature on the day of occurrence was nearly always above 85° F. Very few deaths resulted when the maximum of the day was less than 95° F., and in these cases the air moisture was high.

Air temperatures were found to affect the incidence of heat-stroke as follows :—

Temperatures of 95°–100° F. were dangerous only with high air moisture.

Temperatures of 100°–105° F. were dangerous with moderate air moisture.

Temperatures of 105° F. and over were dangerous even with only 30–50 per cent. of relative air moisture.

He found that 74 per cent. of the cases occurred between noon and 8 p.m. ; none occurred between midnight and 4 a.m. ; the remaining 26 per cent. happened between 8 p.m. and midnight or between 4 a.m. and noon.

The association with high wet-bulb readings was striking—viz.

63·2 per cent. when the wet-bulb temperature was over 79° F.
35·4 ,, ,, ,, ,, ,, 71°–79° F.
1·4 ,, ,, ,, ,, ,, 68°–70° F.

Hutchinson made an interesting analysis of cases of heat-fever among soldiers in Allahabad over a series of years. He found that the great majority of cases occurred towards the end of prolonged spells of excessively hot weather. A few days of very hot weather could be tolerated, but when the heat-wave lasted for three or four weeks there was a regular epidemic of cases towards the end of the period.

All the evidence goes to show that heat-fever results from atmospheric conditions in which the heat-regulating mechanism becomes over-taxed and so fails to keep the body below the temperature at which damage is done to the tissues, especially the nerve cells.

Conditions which Conduce to Heat-Fever

Experimental evidence and the observation of human cases go to show that the following factors are of importance :—

High air temperature.

High air moisture when associated with high air temperature.

Stillness of the air (diminishes the heat-loss caused by evaporation).

Muscular exertion (causes increased heat-production up to five or six times as much as in the resting condition).

Warm and tight clothing (interferes with heat-loss).

Alcohol. (Heat-fever picks out the alcoholics. Total abstainers are much less likely to be attacked, and the fatalities among those who are attacked are much fewer.)

Disease and bodily weakness. (Persons who have malaria, dengue

hurried respiration which may be stertorous. There is a feeling of constriction of the chest, the headache is intense. The knee-jerks are diminished or absent, the urine is scanty and albuminous.

(3) Advanced Stage of Coma. If the patient does not come under energetic treatment at an early stage, he goes on to the state of coma. The temperature is still higher and may be 108°-112° F., though it sometimes shows rapid fluctuations, coming down several degrees for a short time and shooting up again. The patient is usually unconscious, but may be delirious ; he may have epileptiform or tetanic convulsions. The pupils are contracted or dilated and are insensitive to light ; the corneal reflex is lost. The pulse is small, thready and irregular ; the knee-jerks are lost ; the breathing is hurried and may be of the Cheyne-Stokes type. The skin often becomes moist and clammy and the face cyanosed. *Stools are sometimes passed in the bedclothes.* Death results from asphyxia.

Exceptional Types. No two cases are quite similar, and the picture may be complicated by the co-existence of other diseases like malaria, dengue, typhoid fever, etc.

Three special types have been described : (1) **The Cardiac.** Usually there has been some previous lesion of the heart ; the patient gets a sudden pain in the cardiac region, the pulse is small and feeble ; death results from syncope. (2) **Pulmonary.** In this there is congestion or œdema of the lungs with dyspnœa and cyanosis ; crepitant râles are heard all over the lungs, but especially over the bases. There is usually some congestion of the bases of the lungs in severe cases. (3) **Cerebral.** In most cases of severe heat-fever cerebral manifestations are striking, such as coma, delirium, convulsions, etc. A wild impulse to commit suicide, especially by drowning, is not infrequent, or the patient may rush about wildly like a person who has run "amok."

Variations in Severity. The disease when untreated usually goes on to the severe form, but the temperature sometimes does not rise above 103°-104° F., and if energetic treatment is carried out in the early stages the attack seldom becomes severe.

Course of the Disease. Assuming that proper treatment has been carried out early, the patient will usually be out of danger in a day or two. As a rule there is irregular low fever for several days, but unless the temperature rises above 102° F. there is no need for alarm. During the first twenty-four hours the patient should be regarded as in grave danger until the temperature has remained nearly normal for several hours and the general condition is satisfactory.

Sequelæ. In mild cases there are no bad after-effects, but when very high body temperatures have occurred the patient is left in a permanently damaged condition both physically and mentally. Dementia follows in about 10 per cent. of severe cases and suicide in 5 per cent. ; most patients whose temperature has been over 108° F.

In the historical cases in which numerous deaths have occurred among people confined in small rooms during hot weather, the cause of the high mortality was heat-stroke rather than suffocation.

Pathology and Morbid Anatomy

The actual mechanism by which the body is damaged by high temperatures is not clearly understood, but it seems likely that the structural changes are brought about by the direct action of heat on the tissues.

The chief changes found in the body after death are :—

There is congestion of all the viscera and of the dependent parts of the body, sometimes accompanied by petechial hæmorrhages. Hæmorrhagic pulmonary œdema is common. The meninges are often congested and œdematous.

Immediately after death the left ventricle is found to be firmly contracted, soon it becomes flaccid. The blood remains fluid and dark, almost like tar. The muscles are brownish-red ; rigor mortis sets in rapidly, and so also do the other post-mortem changes which appear so soon after death that it is often difficult to decide whether the tissue changes have occurred before or after death, but it seems likely that some degree of coagulation of the muscle fibres and degenerative changes of the nerve cells and fibrils are caused by the high temperature reached before death. In some cases, however, the temperature of the body has been found to continue to rise for a short time after death.

Bacteria of various kinds may be found in blood cultures, but the same thing happens in the cases of death from starvation, cold and other causes, so there is no reason to believe that the bacteria have been concerned in causing the disease.

Symptoms

(1) The Early Stage is the most important of all ; the disease can be arrested if its onset is detected. Common early symptoms are, frequent passage of small quantities of urine, dryness and heat of the skin, and thirst. There is often a feeling of constriction of the chest, with headache, vertigo, photophobia, and drowsiness. The face is often flushed, but may be pale. The conjunctivæ are usually red, and the pupils contracted. Any combination of these symptoms should arouse suspicion when the weather conditions are conducive to heat-fever.

(2) Middle Stage of Excitement. Unfortunately, it usually happens that the disease is not detected till this stage is reached and the temperature has already risen to 104°–107° F., or more ; the early symptoms still persist, but have become more severe ; there is mental excitement, sometimes delirium or convulsions, restlessness, hot and burning skin, contracted pupils, irregular and rapid pulse and

The average fatality rate is about 25 per cent., but figures of average death rates are of little significance in a disease which has such variations in severity as heat-fever. *With early diagnosis and proper treatment, death should rarely occur.*

Unfavourable features are alcoholism, debility, old age, co-existence of another disease and previous disease of the heart, kidneys or lungs. Complete loss of the knee-jerks is a bad sign; their return is a good omen.

The **Prognosis** for ultimate recovery depends chiefly on the duration and height of the fever, on the patient's previous state of health, age, and habits of life.

Treatment. Promptness and energy are called for. Loosen the clothing, place the patient in a cool place, douche him freely with cold water, and fan him vigorously.

Having taken these steps as first-aid treatment, the next thing is to make arrangements for the systematic lowering of the temperature, and for frequently repeated observations of the rectal temperature as a guide to the proper treatment.

Cover the naked body with a sheet soaked in cold water and cause a fan to play vigorously on the patient, who should be placed, if possible, on an iron bedstead covered only with permeable matting. Ice is useful for local application to the head and inguinal regions, preferably by ice-caps. When the air is moist a cold bath is the best way of lowering the body temperature; ice may be needed to cool the water, but an icy cold bath is not desirable; some observers claim that a bath at a temperature of only a few degrees below body heat is better and safer. Constant massage of the limbs should be kept up to maintain the circulation.

When the rectal temperature has fallen to 102° F., dry the patient, put him in bed under a light blanket, and apply an ice-cap to his head. Continue light massage to the limbs, take the rectal temperature every fifteen minutes. If the temperature continues to fall, apply hot bottles to the limbs and body and raise the foot of the bed. Keep the patient under close observation till his condition becomes quite normal. Any rise of temperature must be dealt with promptly, sudden recrudescence of the symptoms may occur without warning.

Cold enemata are of considerable value; their chief drawback is that they interfere with the observation of the rectal temperature, but in some cases they are necessary in spite of this objection.

Other Methods of Treatment. When the pulse is feeble subcutaneous injections of ether and camphor are highly praised by some medical men. Caffeine is also recommended. Intravenous salines have been used, and L. Rogers suggests alkaline saline at a temperature of 60° F. The formula is: sodium chloride, 90 grains; calcium chloride, 4 grains; and sodium bicarbonate, 160 grains; to a pint of water. This can be given intravenously or by the rectum; if given by the

are left with an enfeebled brain—there is loss of memory, irritability, and intolerance of heat. In all severe cases it must be assumed that the patient is likely to suffer from a greater or less degree of permanent disability which will prevent him from carrying out work of a responsible nature. The mental changes are often like those occurring in senility. Severe headache and convulsive seizures may persist for weeks or months.

Diagnosis. The most important point is to realise the likelihood of occurrence of heat-fever when the weather conditions are trying. One of the most common mistakes is to overlook the onset of the disease because the patient has already been suffering from malaria or some other fever, or has recently had a rise of temperature due to *another cause.*

The safe rule is to suspect heat-fever in all cases in which the weather conditions and the symptoms are in keeping with the diagnosis; in such cases, start suitable treatment, and at the same time make a thorough search for other possible causes of the high temperature. To delay treatment because of doubts as to whether the patient has heat-fever or some other disease may be fatal. Whatever the cause of hyperpyrexia, the temperature must be brought down to safe limits without delay.

From *malaria* the diagnosis is by blood examination. From *dengue* and *sandfly fever* the diagnosis may be difficult or impossible at first, but the treatment of hyperpyrexia will be the same in both cases, and later progress will soon make the nature of the disease clear.

In *uræmia* and *diabetic coma* the urine will give a clue to the condition, even if the temperature leaves room for doubt.

From *cerebral apoplexy* with fever the diagnosis consists in noting that the fever has been preceded by loss of consciousness in apoplexy whereas in heat-fever the coma follows the fever. Also there is usually evidence of localised paralysis in apoplexy.

From *cerebro-spinal meningitis.* In this disease the temperature is seldom so high and the head retraction is fairly characteristic, but lumbar puncture is desirable in all doubtful cases.

Prognosis. This depends very much on the height reached by the temperature before treatment has brought it under control. In a series of cases in which the body temperature was less than 107° F., the fatality rate was 8·3 per cent. ; when the temperature was 107°–109° F., it was 29·2 per cent. ; in another group in which the body temperature was over 109° F., it was 69·2 per cent.

L. Rogers, in the General Hospital, Calcutta, found that the duration of unconsciousness before treatment was started gave a valuable clue to the prognosis. Patients who had been unconscious for more than three hours never recovered ; all who had been unconscious for less than an hour and a half recovered. Of those in the intermediate category some recovered and some died.

Major operations should be postponed except in urgent cases unless the hospital has a cooled operating-room and ward. A close watch must be kept on all patients during heat-waves, their temperature should be taken frequently and a sharp lookout kept for such warning features as a hot dry skin, frequent urination, headache and giddiness.

Those who have charge of inexperienced troops or other persons in hot weather should ensure that everyone is instructed in the means of preventing heat effects and see that the instructions are obeyed; most of the attacks of heat-fever and heat-exhaustion result from ignorance and carelessness. A warning should be given of the need to report at once the occurrence of any of the premonitory symptoms of heat-fever.

Railway journeys in extreme heat are specially dangerous; a plentiful supply of water for drinking and cooling the body is more important than the provision of ice which, however, is useful when available in large quantities.

A simple test is available for detecting any inadequacy in the amount of salt intake. Ten drops of urine are placed in a small test tube and one drop of a 20 per cent. solution of potassium chromate is added; with the same dropper, after washing it, a 2·9 per cent. solution of nitrate of silver is added drop by drop; the test tube is shaken after the addition of each drop. The number of drops needed to cause a brown colour in the mixture shows the number of grammes of sodium chloride in each litre of urine. Normally 8 or 9 drops should be needed, if the number is less than 4 there is a considerable deficiency of chlorides.

The total daily output of the urine should be taken into account; when this is large a moderate reduction in the amount of sodium chloride in each litre is of less significance.

II. Heat-Exhaustion

Definition. The types of heat-effect in which the chief features are physical and mental exhaustion are called heat-exhaustion. There are two distinct types: (*a*) the classical or "hidrotic" in which the skin is moist and cool and (*b*) the "anhidrotic" in which the skin of the greater part of the body is dry and burning. The latter type has only recently been recognised but it has important features which necessitate its classification as a different clinical condition.

Classical or Hidrotic Heat-Exhaustion

Definition. The type of heat-effect in which exhaustion is associated with continued activity of the sweat glands.

Clinical Features. After a period of exposure to excessive atmospheric heat, often combined with moisture, the patient becomes lethargic and suffers from giddiness and headache; sometimes there is nausea and vomiting. If the patient is kept at rest in cool conditions he soon recovers, but even mild attacks like these should be taken

bowel, the dose can be repeated at intervals. If there is cyanosis with engorgement of the veins of the neck, oxygen and blood-letting are valuable. As soon as the patient can swallow he should be made to take frequent sips of water or freshly-prepared lemonade to which sodium chloride is added in the proportion of 10 grains to the pint. When there are signs of dehydration, such as a high red-cell count, scanty urine with low chlorides, or a low blood pressure, plenty of fluids should be given, intravenously if necessary, but in this case a close watch must be kept for signs of pulmonary œdema. Lumbar puncture and the slow withdrawal of 20 c.c. or more of fluid is valuable in some severe cases.

Artificial respiration may be necessary. Vantalon recommends rhythmical traction of the tongue combined with rhythmical applications of iced water to the face and chest as being the best means of restoring respiration.

The suspicion of malaria should always be present ; in doubtful cases treatment suitable for cerebral malaria should be given.

Treatment in Convalescence. Perfect rest in a cool and quiet room is essential ; the patient must be treated on the lines suitable for cerebral concussion. The bowels are kept open by mild laxatives ; the diet should be light and nutritious. When the patient is fit to travel he should be sent to a cool climate, and if his attack has been severe he must be forbidden to return to the tropics. All excitement and fatigue must be avoided for several weeks. Rawling advocates subtemporal decompression in all cases in which severe headache with convulsions persist for three months ; these symptoms are due to cerebral œdema, which leads to high intracranial pressure, and so there is usually a slow pulse and persistent vomiting. Out of seven such cases, immediate and lasting improvement resulted in six.

Alcohol is forbidden during convalescence and for a long time after recovery, except in the case of persons who are so addicted to the drug that they would be harmed by deprivation. Life in cheerful but quiet and healthy surroundings is recommended.

Prevention. The first essential is to recognise the existence of dangerous climatic conditions, especially a prolonged spell of excessively hot weather.

During such weather all the controllable factors already described as being conducive to heat-fever must receive attention, especially the avoidance of exertion in the heat of the day, strict moderation in the use of alcohol, or still better total abstinence ; a plentiful intake of water, up to 10 pints or more, to which 10 grains of common salt are added to each pint ; $\frac{1}{2}$–$\frac{3}{4}$ oz. of salt is needed daily.

The artificial cooling of rooms, barracks and especially of hospital wards is a necessity rather than a luxury in very hot climates. There should at least be cool wards for patients suffering from fever or debilitating illness and for those who need operative treatment.

Major operations should be postponed except in urgent cases unless the hospital has a cooled operating-room and ward. A close watch must be kept on all patients during heat-waves, their temperature should be taken frequently and a sharp lookout kept for such warning features as a hot dry skin, frequent urination, headache and giddiness.

Those who have charge of inexperienced troops or other persons in hot weather should ensure that everyone is instructed in the means of preventing heat effects and see that the instructions are obeyed; most of the attacks of heat-fever and heat-exhaustion result from ignorance and carelessness. A warning should be given of the need to report at once the occurrence of any of the premonitory symptoms of heat-fever.

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seriously, they indicate failure of the heat-regulating mechanism to cope with the existing environment and unless this is changed for the better by rest in cool surroundings the symptoms are likely to become aggravated and a state of shock or collapse may ensue.

The physical signs are : a rapid pulse, a low systolic blood pressure, a pale clammy and cool skin. The temperature may be subnormal though sometimes it is slightly raised. The chloride content of the urine is considerably or greatly diminished and there may be muscular cramps.

Prevention is on the same lines as are suitable for heat-fever.

Treatment is by complete rest in cool surroundings and by giving plenty of fluid containing 10 grains to the pint of sodium chloride and sweetened with glucose. Additional salt is given in quantities suitable to the degree of chloride deficiency found in the urine. A light nourishing diet rich in vitamins is given. In severe attacks intravenous salines with 5 per cent. glucose and 2 per cent. bicarbonate of soda, and treatment suitable for shock may be needed.

The temperature must be watched carefully as some cases are early stages of heat-fever.

Anhidrotic Heat-Exhaustion

This well defined type of heat-exhaustion was first described by Wolkin *et al.* in 1944 under the name " thermogenic anhidrosis." It occurred among American troops training in the American Desert. A similar condition was described in 1945 by O'Brien *et al.* in North Australia and New Guinea, and by Ladell *et al.* in Iraq. Horne *et al.* described outbreaks in Karachi and Cawnpore (Kanpur) in India. All the cases occurred among troops training in hot weather.

The chief features were the cessation of sweating over the greater part of the body after a previous period of excessive sweating, usually accompanied by prickly heat, and the absence of any appreciable diminution of the chlorides in the blood and urine.

The symptoms were much the same as in the classical type of heat-exhaustion except that nausea and vomiting did not occur and a sensation of burning of the skin was a feature of the illness. The temperature of the body was often raised to 100° F.

The face, hands and feet continued to sweat, but the skin of the rest of the body was dry and was in a condition of " goose-flesh " produced by the drying up and whitening of the previously inflamed sweat glands. The administration of chlorides did not cause any improvement in the condition, otherwise the treatment suitable for heat-exhaustion with sweating was equally effective. Polyuria was frequent in some of the outbreaks.

Apparently the drying up of the sweat glands resulted from damage caused by a period of excessive sweating, which may have been promoted by the large intake of salt now customary among troops in hot

climates and which may have enabled the men to resist the adverse effects of heat longer than they otherwise could have done.

If the troops had not been under close supervision some of them would probably have developed heat fever; anhidrosis and polyuria have long been recognised as being premonitory symptoms of that disease.

Persons who have suffered from either type of heat-exhaustion in conditions necessitated by their duties must be regarded as unfit for service in hot climates unless it can be arranged that they can avoid the adverse environmental factors responsible for causing the attack

III. Heat-Cramp

Heat-cramp is the type of heat effect in which painful spasm of the muscles is the chief feature; it is specially common among ship stokers and other persons who have to do hard work in very hot atmospheric conditions The cause is dehydration of the blood resulting from loss of chlorides due to excessive sweating. The muscles most often affected are those of the arms and legs; the pain may be agonising: the muscles are hard to the touch, being in a state of intense spasmodic contraction

Morphia is often needed to relieve the unbearable pain; the saline content of the blood is restored by giving water containing 10 grains of common salt to the pint and 5 grain tablets of salt at intervals so as to make up the salt intake to ¾ oz. daily. In very severe attacks intravenous saline may be needed. To prevent recurrence a high salt intake is necessary, plenty of water with added salt should be taken and salt tablets should be sucked to maintain the total intake stated above.

DISEASES CAUSED BY LIGHT

I. Solar Dermatitis

This is an inflammation of the skin caused by excessive exposure to the ultra-violet rays of the sun. Even cold rays reflected from snow can cause the disease; so also can the rays of a mercury-vapour or arc lamp.

The non-pigmented skin of Europeans is very sensitive to ultra-violet rays till acclimatisation has taken place. French doctors call this condition "*coup de soleil*" (sun-stroke).

Moderate exposure to ultra-violet rays is healthful, but over-exposure causes dermatitis, which is more or less severe according to the dosage of the rays and the sensitiveness of the skin.

When the skin has been exposed to the rays, nothing is felt for a few hours; then there is a sensation of smarting or burning, with redness, heat, and œdema of the part of the skin which has been exposed. After two or three days desquamation follows, and there is

increased pigmentation which may last for a long time. After recovery from an attack the affected skin is much less sensitive than before.

In severe cases blistering may occur, and if a large area of the body is affected there is malaise and a rise of temperature due to absorption of the toxic products resulting from damage to the tissues. A few deaths have been reported. Persons exposed to strong sunlight for many years may suffer from a pigmented and warty condition of the skin, or even from epithelioma in extreme cases.

Treatment. A soothing application like calamine lotion followed by cold cream is a suitable treatment.

Prevention. Any kind of clothing, however thin, is enough to cut out a large proportion of the ultra-violet rays. An umbrella may be needed, and when walking over snow, a veil is sometimes necessary to protect the face from the potent reflected rays.

II. Light-Stroke and Glare-Headache

When excessive light falls on the retina, temporary or permanent blindness of part of the retina may result.

The most usual result of glare is headache, due to irritation of the retina by bright light. Dark glasses are the well-known means of prevention ; they should be used by all who are exposed to excessive glare. Neutral-tinted or green-yellow glasses may be used according to taste. Any kind of ordinary glass cuts off most of the ultra-violet rays and so prevents them from damaging the retina, but tinted glasses are desirable because they protect also against headache and damage to the retina due to glare.

III. Night-Blindness

In this disease there is diminution of sensitiveness of the retina caused by prolonged over-stimulation by bright light ; retinal defects due to malnutrition or disease are predisposing factors. Deficiency of vitamin A in the diet is an important causal factor in many cases.

Malaria and diphtheria are specially liable to be associated with night-blindness. Xerophthalmia is a frequent concomitant of the form of the disease associated with diet deficiency.

The sensitiveness of the eye to weak light is greatly reduced in night-blindness ; perception of light may be reduced to less than 1 per cent. of the normal. The patient can see perfectly by day, but in the dusk he suddenly finds himself unable to distinguish any objects.

Diagnosis. Ophthalmoscopic examination will exclude retinitis pigmentosa and other gross retinal disease. The diagnosis is difficult in cases of malingering. The sudden failure to distinguish all the letters or figures on a test-card when the intensity of the light is diminished below a certain point is a feature of night-blindness whereas

normal persons first become unable to see small letters and gradually fail to see the larger ones when the light is dimmed. Malingerers who are unaware of this feature of the disease will usually pretend to be unable to see small letters while they can still distinguish the large ones.

Treatment. The traditional cure by eating the liver of goats, etc., is useful in cases in which there is defective nourishment; cod-liver oil is also of value; dark glasses should be worn in the daytime.

Attention to the general health is important in those cases in which there is a lowering of vitality from disease or malnutrition.

J. W. D. MEGAW

CHAPTER XXVI

THE INCIDENCE OF GENERAL DISEASES IN THE TROPICS

THE practitioner in the tropics requires to know what variations in the incidence of the common diseases of world-wide distribution he is likely to meet with as compared with experience in the temperate zone, but he will find little information on this subject in text-books. The writer spent much time in analysing some 4,000 post-mortems during thirty-seven years, including 1,600 of his own, in Calcutta, and recorded his results in a series of papers in the *Indian Medical Gazette* from 1908 to 1914, and in the Finlayson lectures in the *Glasgow Medical Journal* of 1925, and his main conclusions have been since confirmed by a similar inquiry in Bombay by Gharpure, 1928, so a short summary may be of use to workers in the tropics, although, doubtless, local experience will suggest modifications as regards some of the details. The original articles may be referred to for fuller information on this somewhat neglected aspect of practice in the tropics. For comparison with the 1,600 Calcutta post-mortems, the percentages of the deaths from different groups of diseases were worked out from 1,000 post-mortems at St. Mary's Hospital, London ; these data serve to bring out the principal differences in their incidence in the two areas, and present many points of interest. The vital statistics of Calcutta were also studied, and gave remarkably similar data to those derived from the post-mortem series there ; this indicates that the post-mortem data furnished reliable indications regarding the general population of the largest city in India, with over 1,000,000 inhabitants, and the similarity of the data in Bombay, with nearly the same population, adds weight to the conclusions arrived at.

No reliable figures are available for the rural population, but it may be noted that many of the patients in the Calcutta hospitals come from rural areas.

Two additional columns have been added in Table II ; the figures in these have been prepared in such a way so as to conform as closely as possible with those in the first two columns.

The data dealing with the United Fruit Company were prepared from the returns of the causes of the 621 deaths which occurred in the hospitals of the company in 1927. The localities concerned are Cuba, Costa Rica, Jamaica, Colombia, Panama and Honduras. The figures for the Philippines deal with 1,361 deaths in the Philippine General Hospital in 1925.

These additional figures are of interest in two respects ; they show that most of the cosmopolitan diseases have approximately the same incidence in the tropics, but they also show that remarkable variations occur which are due partly to differences in the incidence of the

diseases, but also partly to differences in the methods of classifying the diseases.

Proportion of Deaths from Tropical Diseases in Calcutta. Both the post-mortem series and the vital statistics of Calcutta show that about one-third of the deaths are due to the diseases specially prevalent in hot climates, so that the remaining two-thirds are well worthy of study from the point of view of this article. Of the 33 per cent. of deaths from tropical diseases, 10 per cent. were due to the tropical fevers, malaria (1·56), kala-azar (8·06), and plague (0·37); 9·69 per cent. to cholera (mostly before the modern methods of treatment were in use); 10·5 per cent. to dysenteries, with a preponderance of amœbic cases (5·69), and 2·69 per cent. to amœbic liver abscess, leaving under 2 per cent. for other tropical diseases such as beri-beri (0·37) and ancylostomiasis (0·19). Thus, fevers and bowel diseases account for the vast majority of the fatalities in this group; this fully justifies the large proportion of space allotted to those groups of diseases in this book. Owing to Calcutta being well drained, malarial cases rarely originate in the city, so the malarial data afford no indication of the rural rate, which is many times greater than in Calcutta itself. Few children are admitted to the Calcutta Medical Hospital, and post-mortems are very rarely obtained on young children, although the infantile mortality is extraordinarily high in Calcutta and India in general. For this reason the deaths in children under five years of age have been omitted in the comparison between the tables of the vital statistics of the Calcutta Corporation, so as to make the data comparable with those of the post-mortem series, with the result that the figures of the different groups of cases mentioned above do not vary as much as 1 per cent. in any of them, with the exception that "infantile liver" (2·48) figures are higher in the Corporation figures owing to the fact that these cases are rarely seen on the post-mortem table; the two sets of data are, therefore, so closely conformable that they may be regarded as reliable.

The Age Incidence of Medical Post-Mortems in India and London. The age distribution of over 4,000 Calcutta subjects showed that there were very few children under ten years, and considerably fewer persons over fifty years of age, as compared with the London data. To get a true comparison the children under ten years were omitted from each series, as they are rarely admitted to Indian hospitals, and the data then showed in the Calcutta series 21·7, 8·0 and 2·0 per cent. respectively in persons over forty, fifty and sixty years of age, against 58·4, 38·5 and 14·4 per cent. in the London series. These remarkable differences must be taken into account in estimating the prevalence of certain diseases, such as cancer, in the two series of data.

Variations in the Percentages of Deaths in the Main Groups of Disease. Table I gives the data regarding the main groups of non-tropical diseases in the London post-mortems, the Calcutta post-mortems and the Calcutta vital statistics respectively; these show

the following main differences of the incidence in British and Indian conditions.

The most striking differences in Table I are the excess in Calcutta of the deaths due to general diseases, tuberculosis, respiratory and digestive diseases, and the low mortality from diseases of the circulatory and nervous systems and from malignant diseases as compared with the

TABLE I. PERCENTAGES OF DEATHS IN THE MAIN GROUPS OF DISEASES

Group	London P.-M.'s	Calcutta P.-M.'s	Calcutta Vital Statistics (less Children under Five Years)
General	6·1	9·23	9·5
Tuberculosis	13·4	21·93	21·5
Respiratory	16·8	27·13	48·7
Circulatory	20·3	10·50	5·4
Digestive	7·5	12·00	7·2
Urinary	8·6	6·35	1·8
Nervous	11·9	7·41	4·1
Malignant disease	13·8	4·59	1·2
Remainder	1·6	0·84	—

London series. The Calcutta vital statistics agree closely with the post-mortem ones, so these variations require further elucidation. It will be convenient to give the most important detailed data of the actual diseases which differ most widely in Table II given on p. 519.

GENERAL DISEASES

The greater frequency of fatal **anæmia** in a debilitating tropical country is only what was to be expected. **Leukæmia** caused 1·7 per cent. of the deaths in London, against 0·27 in Calcutta, but the writer met with several cases clinically in India. **Diabetes** is very common in the well-to-do, educated Indians, who consume much starchy food and sugar, but the figures in Table II show this disease to be much less common in the poorer hospital class of Indians than in the London series. **Diphtheria** is common in Calcutta, but rather rare in India as a whole. The mild cases are often overlooked, but severe cases, followed by post-diphtheritic paralysis, are often seen, so the disease should be regarded as a possibility in most places in the tropics. **Septicæmic** diseases are far more commonly fatal in the Calcutta medical post-mortems than in London, and the writer's experience bears out the data in Table II on this point. **Tetanus** of the idiopathic type caused 2 per cent. of the Calcutta deaths, against only 0·1 per cent. in London. The writer found that the insertion of a little Calcutta street-dust under the skin of a rat produced the disease in five out of six of the

TABLE II. COMPARISON OF PERCENTAGES OF DEATHS FROM CERTAIN DISEASES

Group and Disease	London P.M.s	Calcutta P.M.s		United Fruit Co.	[illegible] Gen. Hosp.
General Diseases.					
(1) Anaemia . .	1·5	2·34	—	1·2	4·7
(2) Diabetes .	0·7	0·27	—	—	—
(3) Septicaemias. .	0·5	3·00	—	6·3	3·8
(4) Tetanus .	0·4	2·05	—	1·8	1·0
(5) Typhoid fever .	0·3	1·21	—	?	?
Tuberculosis.					
(1) General . .	3·5	3·09	—	?	?
(2) Meningitis . .	2·4	1·01	—	?	?
(3) Pulmonary . .	5·4	16·10	—	12·6	7·5
(4) Primary intestinal	0·0	1·01	—	?	?
Respiratory Diseases.					
(1) Lobar pneumonia	4·2	16·03	—	22·3	3·2
(2) Broncho-pneumonia	6·1	5·80	—	7·5	11·0
(3) Bronchitis . .	4·7	3·00	—	0·2	0·65
Circulatory Diseases.					
(1) Ulcerative endocarditis . .	2·6	1·50	Acute endocarditis.	1·4	0·65
(2) Rheumatic endocarditis . .	3·7	0·00	—	—	—
(3) Aortic valve disease	2·6	2·73	Chronic endocarditis and other heart diseases.	7·1	13·4
(4) Mitral valve disease	4·3	0·93			
(5) Aneurism . .	3·2	1·59	—	?	?
Digestive System Diseases.					
(1) Gastric and duodenal ulcers .	2·1	0·92	—	1·4	0·65
(2) Cirrhosis of liver .	1·3	5·91	—	0·6	1·0
			Other liver diseases.	1·4	4·0
Renal.					
(1) Parenchymatous nephritis . .	2·3	1·96	Acute and chronic nephritis.	8·6	10·5
(2) Interstitial nephritis . . .	5·4	3·46			
Nervous System.					
(1) Meningitis (non-tuberculosis) .	2·4	3·29	Epidemic C.S. meningitis.	0·8	1·4
			Meningitis other forms	3·9	—
(2) Apoplexy . .	6·2	1·96	—	1·6	2·2

animals; this bears out the greater danger of tetanus in the tropics, and it is also not rare in the surgical wards, but was reduced by the prophylactic use of anti-tetanic serum in cases of contaminated wounds. The Calcutta vital statistics show the appalling figure of 6·04 per cent. of deaths at all ages, and 1·1 per cent. in subjects over five years of age. The first figure is due to the fact that tetanus neonatorum very frequently follows the application of cow-dung and other filthy dressings to the umbilical cord by ignorant midwives in India. The danger of tetanus following on *hypodermic and intramuscular infection* of quinine has already been emphasised. **Typhoid fever** is well known to be very frequent in India, but it was not until the use of the Widal test by the writer in Calcutta in 1900, and by others elsewhere in India, that the long-held fallacy that the people of India rarely suffered from the disease was exposed. The cases had previously been shown under the elastic heading of "remittent fever." The necessity for all Europeans to be inoculated against typhoid and the paratyphoids before going to the tropics is thus evident.

Tuberculosis. In recent years attention has been drawn by Lyle Cummins and others to the fact that pulmonary tuberculosis is both very common and runs a very acute and fatal course in the tropics, but the extreme importance of the tuberculosis problem in India and other warm climates has only recently been fully realised. In 1904, during an inquiry into the true causes of the deaths returned as due to "fever" in a malarious area of Bengal, the writer obtained clear evidence that phthisis accounted for at least 9 per cent. (90 per mille) of the total deaths in the villages. In 1909, an analysis of over 3,000 Calcutta post-mortems showed 18·3 per cent. of the deaths to have been due to active tuberculosis, and in 7·2 per cent. more old, latent tubercle of the lungs was found, or a total of 25·5 per cent. with gross tubercular lesions. On the other hand, surgical tuberculosis cases were shown to be far more rare in Great Britain, although they have since been shown to be less uncommon in the Punjab, with a cold winter, and some other parts of India. The data in Table II show the fatal cases of phthisis to have been three times more frequent in the Calcutta than in the London series of post-mortems, and this difference is confirmed by the Calcutta vital statistics, which show the still higher figure of 20·4 per cent. of the deaths to be from phthisis in subjects over five years of age. The disease is also known to be more common among females than males; it is highest in Muslim females, who suffer most from the purdah system. The rapidity of the course of the disease in India appears to be due mainly to lower resisting power of the subjects, as generalised tuberculosis is quite as common in London as in Calcutta autopsies. The joint-family system of the Hindus, with several generations living in one huge barrack-like building built round a small central courtyard, favours the spread of the infection. A. Powell has recorded equally serious prevalence in Bombay; he

showed that the police recruits from villages frequently became infected in the city of Bombay, and that the disease was on the increase, so that the urgency of the problem can scarcely be exaggerated. The disease is very common in all large centres of population in India, and less common in the rural areas, but there is good evidence that it is increasing in frequency all over India. The probable reason is that the stress of population is increasing to such an extent that there is not enough nourishment for the people. The inhabitants of tropical countries show a lower degree of resistance to the disease than those of temperate climates; this is partly due to the remarkable rarity of bovine infection which immunises many children in Europe.

It is notorious that the people of places where the disease is absent show little resistance to the infection which they contract when they migrate to the large towns or when they join the army or police forces.

It is possible that the rapid course of the disease in recent arrivals in large cities is partly due to the absence of the immunity which results from both bovine and human infection in childhood in European countries, but it is also due in great measure to the low resisting powers of the under-nourished and disease-ridden people of the tropics.

Primary Intestinal Tuberculosis shows the remarkable incidence of 1·04 in the Calcutta series, against *nil* in the one thousand London autopsies. The writer had long ago been struck by this incidence, and inoculation of animals showed that they were due to the human and not to the bovine type of tubercle bacillus; this is in accordance with the well-known great rarity of bovine tubercle in Indian cattle, about 0·5 per cent. in Calcutta, and *nil* in over 200 cattle autopsies in the Kumaon Hills, in the course of the writer's rinderpest investigation in 1899. These facts also explain the comparative rarity of surgical tuberculosis in Bengal, and the primary intestinal cases are probably due to ingestion of food contaminated with the sputum of phthisical patients. Tuberculosis meningitis was more frequent in the London series in which there was a larger proportion of children, but it is also seen in children in India.

Respiratory Diseases (other than phthisis). Here again we meet with the very striking fact that the lobar pneumonia deaths formed 16·10 of the total, and 17·9 per cent. in the vital statistics of Calcutta, against only 4·2 per cent. in the London series, or almost four times as many in India, in spite of there being no really cold weather in Lower Bengal; and that, too, although only cases which were the primary cause of death are included in the data. **Broncho-pneumonia** was about equally frequent in the two series, but the great majority of the Calcutta cases occurred during the 1918 influenza epidemic, apart from which broncho-pneumonia was rare in Calcutta, largely on account of the few young and old subjects in the series. **Bronchitis** caused a slightly larger proportion of deaths in the London series, also partly due to the age factor.

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mortem room, so the following evidence, based mainly on 1,800 post-mortems during thirty-seven years, requires to be emphasised. In that large series of autopsies there was only one death returned as due to rheumatic endocarditis, and that was in an Anglo-Indian subject who had probably visited a cold climate; there was also only one case of possible rheumatic pericarditis. Moreover, among several thousand specimens in the Calcutta pathological museum, accumulated during eighty years, there was only one described as rheumatic endocarditis in an Indian subject, and that may well have been of pneumococcal or septic origin, as during twenty years' post-mortem experience the writer found all his endocarditis cases to be due to that class of organism. It may, therefore, be held that reliable evidence of the occurrence of rheumatic endocarditis in natives of Bengal is still lacking.

My collaborator, J. W. D. Megaw, who has made a collective investigation into the subject, and has also had a good deal of personal experience in various parts of India, agrees that rheumatic endocarditis is much less common than in Europe, but he has found evidence that it is by no means rare in places like Lucknow, while it occurs not infrequently in some places where the winter season is not really cold.

Ulcerative Endocarditis. On turning once more to Table II, we find 2·6 per cent. of the London and 1·5 per cent. of the Calcutta autopsies showed malignant endocarditis as the primary cause of death; the causal organism in India was usually the pneumococcus, while the gonococcus was isolated in one case. In Calcutta the aortic valve was affected more frequently than the mitral, just the reverse of Osler's experience, probably accounted for by the rarity in Calcutta of rheumatic inflammation of the mitral which predisposes to later ulcerative changes.

Pericarditis. This was more frequent in the Calcutta series, but none of the cases were rheumatic in origin. Pneumococcal infection was the most common cause, for the condition was secondary to pneumonia in 75 per cent. of 102 cases in the thirty-seven years' records, septic infections, often secondary to amœbic liver abscess, in 14, and tubercular in 10 per cent.

Organic Valvular Disease. Aortic valve disease was equally frequent in both series, but the figure for mitral disease was 4·3 per cent. in London and only 0·93 per cent. in Calcutta, or about one-fifth the number; this striking difference is also explained by the rarity of rheumatic fever in Bengal, for the aortic cases were usually due to syphilitic atheroma in Calcutta. This is confirmed by the age incidence of the aortic cases having been much higher than that of the mitral cases in London, but almost the same in Calcutta, and by the fact that half the Calcutta mitral-stenosis cases also showed syphilitic atheroma; this indicates that syphilis, and not rheumatic fever, was the causative factor. There was also a preponderance in males of mitral-stenosis

It is thus evident that phthisis and lobar pneumonia are the most frequent causes of death in Calcutta, more so than any of the so-called tropical diseases. Yet, strange to say, one of the leading physicians of Calcutta, when speaking as a delegate at an international congress in Berlin, in 1892, solemnly declared that phthisis and other lung diseases are rare in natives of India! Could any more striking evidence be produced of the necessity for checking clinical experience by the facts of the post-mortem room, such as are being discussed in this article?

Pneumonia is still more prevalent during the cold winter months in the Punjab and Sind, and the writer has recently shown that this prevalence is associated with the great diurnal variation of the temperature of 30° F. or more, very low absolute *humidity of 0·250 with great drying power, and the low minimum temperature of about freezing point with cold north winds, all resulting in chills predisposing to pneumonia. Huddling together in small unventilated rooms to avoid* the great winter cold may also be a factor here, especially in favouring pneumonia epidemics. The incidence declines from North-West to South-East India coincidently with the progressive amelioration of those adverse climatic factors. He also found that the highest phthisis rates occur in the areas with high humidity in the monsoon months and in areas exposed to the humid monsoon winds in India. **Gangrene** of the lung, following pneumonia, is not rare in India. **Empyema** was about equally common in the London and the Calcutta series. **Abscess** of the lung is very frequent, as the result of the spread of amœbic hepatitis through the diaphragm, usually to the base of the right lung. Nearly all the pneumonia cases are due to the pneumococcus in India; secondary septic pneumonias come next in frequency.

The remarkably high death rate from respiratory infections in the tropics is probably associated with debility caused by previous attacks of malaria and other diseases, by malnutrition and unhygienic habits of life.

Circulatory Diseases. The most striking and interesting feature of this inquiry is the fact that deaths from circulatory diseases in the Indian series are just one-half of those of the London one. The essential cause of this great difference is the remarkable infrequency of rheumatic fever and its sequelæ among the inhabitants of Bengal. As long ago as 1886 Norman Chevers, in his classical *Commentary on Diseases of India*, remarked on the rarity of acute rheumatism in Bengal, and he quotes Malcolmsen as having made a similar observation as regards Madras in 1835, while Morehead noted that it was uncommon in Bombay. Scarlet fever is also very rare in India, especially among the indigenous population, so the two most frequent causes of subsequent organic valvular disease are almost absent from the plains of India, with the result that the whole aspect of cardiac disease is greatly altered; a fact which is not yet sufficiently realised, judging from the frequent mistaken diagnoses revealed in the post-

the liver was nearly five times as frequent in the Calcutta as in the London series, and this is fully borne out by the fact that this condition was met with in no less than 6·9 per cent. of 4,800 Calcutta autopsies against just under 1 per cent. in 3,200 Berlin ones. This subject was fully discussed by the writer in the *Indian Medical Gazette* in 1911, when it was shown that the disease is nearly as frequent in the total-abstaining Mahomedans as in the Hindus, who are not forbidden by their religion to take alcohol. Some cases are secondary to kala-azar, which may cause a peculiar smooth surfaced intercellular cirrhosis described by the writer, but there was no evidence that malaria ever produced a clinically evident cirrhosis of the liver. Schistosome disease is absent from India and infantile biliary cirrhosis very rarely comes to the post-mortem table in India, where under 2 per cent. of all cirrhosis cases were of syphilitic origin. An elaborate analysis of over 4,000 Calcutta post-mortems showed evidence of past dysentery, including scars of old dysentery, in 25 to 30 per cent. of the cirrhosis cases, or 1 to every 3·6 cases of dysentery, although the ratio in the general run of cases, including the cirrhosis ones, was only 1 to 8·56, or less than half as frequent. It was also found that in the more advanced cirrhosis cases scars of old dysentery were most commonly found, probably antecedent to the cirrhosis. It is also of importance to note that cirrhosis of the liver was less common in the European subjects, who suffered much less from dysentery, but took more alcohol than the Indians. All the evidence, therefore, points to old chronic dysentery as the most likely cause of the excessive amount of cirrhosis of the liver in Indians in Calcutta, and it certainly cannot be explained as due to alcohol. The explanation is not far to seek, as the disease was especially associated in the writer's experience with chronic relapsing amœbic dysentery which produces such great fibrous tissue formation around chronic amœbic liver abscesses, so that the frequently recurring non-suppurative amœbic hepatitis may be expected to produce diffuse fibrous tissue formation ending in cirrhosis. It is worthy of note that the Calcutta records show a number of cases of a chronic or encysted amœbic liver abscess in a cirrhotic liver. The practical inference is the necessity for efficient and repeated treatment of amœbic hepatitis and dysentery in order to avert subsequent cirrhosis as well as suppuration in the liver.

My collaborator, J. W. D. Megaw, while agreeing that a non-alcoholic form of cirrhosis of the liver is much more common in India than in Europe, believes that most of the cases of endemic ascites, which run a prolonged course with frequent tappings, are wrongly diagnosed as cirrhosis of the liver. He regards these cases as being due to a chronic peritonitis with fibrotic thickening of the whole of the peritoneum, including that which covers the liver. He regards the peritonitis as being caused by the passage of the irritant toxins of bacillary dysentery through the bowel wall. In a large series of cases

cases in Calcutta, quite contrary to European experience. The whole aspect of valvular disease of the heart in India is thus altered radically by the rarity of rheumatic endocarditis in that country.

Atheroma and Aneurism. Aneurisms were about twice as frequent in the London as in the Calcutta autopsies. An analysis of the age incidence of atheroma in 1,000 Calcutta and 300 London post-mortems showed that marked lesions become common in both series with increasing frequency from the fifth decade of life onwards, so the far larger number of old subjects in the London series accounts for the greater incidence of aneurisms in it. An analysis of 5,900 medical and surgical Calcutta autopsies showed only thirty cases of aneurism (0·5 per cent.) and 31 per cent. of these occurred among the 2·2 per cent. of European subjects, while Muslims were affected twice as often as Hindus. This is in accordance with the stamina and meat-eating habits of these races; the vegetarian Hindus have the lowest blood pressure of the three.

Primary Syphilitic Pulmonary Atheroma. This rare disease, in which there is extensive dilatation of the pulmonary arteries in the lungs—leading to hypertrophy and later fatal dilatation of the right heart with dropsy and hydropericardium, but no valvular disease, is by no means rare in Calcutta, for the writer in 1908 recorded no less than nine cases, one of which he diagnosed correctly during life; they occurred mainly in young females of the prostitute class.

The circulatory diseases in India, therefore, present many points of difference from experience in Europe, which the practitioner in the tropics requires to bear in mind if he is to avoid errors in diagnosis, which Calcutta autopsies have shown to have been very commonly made in India.

A large group of cardiac disease in the tropics does not appear in the returns of death. This includes the senile and other degenerative changes in the myocardium, which are common causes of heart failure. It is impossible to classify cases of cardiac disease in a dogmatic manner in accordance with ætiology, as there are so many complicating factors; for example, in cases of so-called "malignant endocarditis" it is likely that the original damage may sometimes have been done by the organism of rheumatic endocarditis, and that a secondary infection has established itself in the damaged tissues. In atheroma, too, the picture is probably complex in many cases; syphilis may be the sole factor in some cases, but in others it probably combines with other factors which cause arterial degeneration.

Digestive Diseases. Gastric and duodenal ulcers were twice as frequent in the London as in the Calcutta series. This bears out the writer's experience in India, and it may be related to the largely vegetarian diet of Indians, in whom appendicitis is also considerably less frequently seen than among Europeans.

Cirrhosis of the Liver. A more striking fact is that fatal cirrhosis of

5 due to embolism, and 12 classed as cerebral softening, most probably due to thrombosis, as a rule of syphilitic origin. The rarity of cerebral embolism is explained by the rarity of rheumatic endocarditis, and the few cases met with were mostly secondary to malignant endocarditis. The age incidence showed a majority of thrombosis cases in the third and fourth decades of life, and of cerebral hæmorrhage in the fourth and fifth decades. The sex incidence showed a great excess of cases of cerebral hæmorrhage among females in proportion to their numbers, and the excess was closely related to that of granular kidney in females; this indicates the close relationship between the two conditions.

Cerebral tumours in the larger series of 4,800 Indian autopsies showed gummata and gliomata as the most common; tuberculous tumours were also met with, and syphilitic paraplegia was not very rare. Epilepsy only caused four deaths and cerebral abscess was only met with three times. Cysticercosis has been shown (1934) by W. P. MacArthur to be a frequent cause of epilepsy in British soldiers invalided home from India. In such cases superficial cysts may be felt in various parts of the body and more deeply seated calcified ones may be detected by X-ray examination.

Gallstones used to be stated in English text-books to be rare among Indians, but the writer's analysis of 4,544 Calcutta autopsies and 1,200 London ones showed that gallstones are rather more frequent in India than in England. Moreover, in each decade of life from the second on, gallstones were about twice as frequent in females as in males in both series; a fact of some importance in regard to ætiology, as the old theory that the excess in females is due to sedentary habits and tight-lacing certainly does not apply to lower class Indian women, who furnish the autopsy subjects in Calcutta, so the difference appears to lie in some physiological sex difference.

Cancer and other Tumours. It has been stated by some writers that cancer is very rarely seen in indigenous races of the tropics. To test this theory the writer analysed 1,190 tumours examined microscopically in Calcutta and compared the results with 1,000 cases from the St. Mary's Hospital pathological laboratory records. These data, together with the post-mortem series in both countries, throw light on this view and on the differences in the incidence of different forms of tumours met with which are of interest. Table I shows 4·59 per cent. of Calcutta deaths to have been due to malignant disease against 13·8 in London, or a ratio of about 1 to 3. Only 3·3 per cent. of the London cancer cases occurred below the age of forty, and only 24 per cent. below fifty years, and the ratio of Calcutta to London subjects over forty was 1·0 to 2·7, and that of those of over fifty years was 1 to 4·8, so it is clear that the lower Calcutta cancer rate is fully discounted by the age factor.

A classification of the 1,190 Calcutta and the 1,000 London tumours

which were investigated by him there was a history of recent dysentery or diarrhœa in the great majority of the cases. The patients gave a much higher titre of agglutination against the Flexner bacillus than the controls, and in the cases which were examined after death there was a fibrotic thickening of the peritoneum with adhesions between the abdominal viscera, while the liver showed no cirrhosis but only a thickening of the capsule.

Renal Diseases. Parenchymatous nephritis was met with in nearly as large a proportion in the Calcutta as in the London series, but granular kidney was the cause of death in 3·46 per cent. of the Calcutta series and in 5·4 per cent. of the London series. This difference appears to be most closely related to the higher ages of the London subjects, as the proportion of cases increases in both countries with each decade of life, and most rapidly after the age of fifty. An analysis of 4,280 Calcutta post-mortems brought out the fact that Bright's disease as a whole was twice as frequent among meat-eating Europeans as in Indians, and the vegetarian Hindus had the lowest incidence.

The figures for the West Indies and Philippines suggest that nephritis as a whole is more common in the tropics than in cold countries. J. W. D. Megaw has suggested that the toxins of bacillary dysentery may play a part in the causation of nephritis by setting up irritation of the kidneys in the process of elimination.

Other fatal renal diseases were few. Enlarged prostate is rare in India in relationship to the small proportion of elderly autopsy subjects.

Nervous Diseases. Non-tubercular meningitis caused 3·29 per cent. of Calcutta deaths, against 2·4 per cent. of the London autopsies. Among thirteen Indian cases with bacteriological examinations no less than eleven were due to the pneumococcus and two to streptococci. This is of interest in connection with the excess of lobar pneumonia cases in Calcutta. The purulent effusion in pneumococcal cases is chiefly on the upper surface of the brain, but in cerebrospinal fever is more on the under surface ; the latter disease also occurs in scattered outbreaks in India, as shown in the writer's *Fevers in the Tropics*. The foregoing data are confirmed by an analysis of 4,800 Calcutta autopsies with forty-two cases of pneumococcal meningitis, twenty-eight tuberculous cases, thirteen due to strepto- or staphylo-cocci, and fifty-eight unclassified. Most of the unclassified cases were probably also pneumococcal. This is confirmed by the fact that 60 per cent. of the pneumococcal meningitis cases occurred in the four cold-weather months when lobar pneumonia is also most prevalent, and the fewest during the rainy season with least pneumonia.

Apoplexy, on the other hand, was far more frequent in the London series, with 6·2 per cent. of the total deaths against only 1·96 in Calcutta. Among the 4,800 Calcutta autopsies vascular cerebral lesions were the cause of death in 77, or only 1·61 per cent., 34 were cerebral hæmorrhages, 7 subdural hæmorrhages, 19 thrombosis, only

malignant epithelial tumours: these showed excess in India of epithelioma of the skin in relation with the frequency of chronic ulcerative processes. Cancer of the cervix uteri and of the body of the uterus and ovary are all very prevalent in India and a striking point is that the age incidence of cancer of the uterus is about ten years younger than in London The factors which may have a possible bearing on this are the early menstruation, child bearing period and climacteric in Indian women resulting in early cancerous degenerative processes. It is also possible that discharges and secretions may be more irritating to the tissues in hot, moist climates, especially among the poorer and less cleanly classes of women Epithelioma of the penis is also very common in uncircumcised Hindus, but not in the circumcised Mahomedans. Epithelioma of the inside of the cheek often follows chewing betel nut with lime. Primary cancer of the liver furnished 7·7 per cent of the Calcutta, but none of the London series. On the other hand, the London series showed a great excess over the Indian series in cases of cancer of the tongue and floor of the mouth, probably associated with more frequent irritation by bad teeth in Europeans, and of the throat, œsophagus, and especially of the large intestine, with 3·3 per cent of the last against only 0·76 per cent. in Calcutta, possibly associated with the frequent passage of more constipated stools by Europeans Cancer of the breast caused 15·2 per cent. of the London tumours against only 0·8 per cent. in Calcutta, possibly in connection with the tighter clothing worn by European women up to fairly recent times In short, the main variations between the two series are all explainable on the very generally accepted theory that chronic irritation is the most powerful predisposing or exciting cause of cancer, and that when this factor comes prominently into action cancer is quite as frequent in the peoples of India, especially if the age factor is taken into consideration, as in those of Europe. A knowledge of the varieties of such tumours most commonly prevalent in a tropical country like India will enable the practitioner to be on the look out for them. (See Finlayson Lectures (1925) for further details.)

LEONARD ROGERS.

COSMOPOLITAN DISEASES IN THE TROPICS

The statistics compiled by L. Rogers and others give a good idea of the extent to which some of the cosmopolitan diseases prevail in the tropics, but a brief reference to some of these diseases from the clinical point of view is added.

Typhoid Fever

Typhoid and paratyphoid fevers are exceedingly common in many places in the tropics. Paratyphoid A is more common than para-

furnishes further data of interest, which are illustrated by Table III, given on this page.

The first point to be noted is that the total percentage of malignant tumours is practically the same in both series, with a slight excess in the Indian one. It is also of great interest to observe that the proportion of both simple and malignant connective tissue tumours is nearly twice as high in the Calcutta series, and the percentage of both the simple and the malignant epithelial tumours is far higher in the London cases. This fact lends strong support to the view now so widely held that there is no very hard-and-fast line between simple and malignant tumours, but the simple ones are liable to take on malignancy after a time. Simple connective tissue ones become sarcomatous, and

TABLE III. INCIDENCE OF TUMOURS IN 1,190 CALCUTTA AND 1,000 LONDON CASES

INNOCENT TUMOURS

Class of Tumour.	Calcutta Percentage.	London Percentage.
(1) Connective tissue	24·45	14·7
(2) Cysts.	9·25	13·0
(3) Epithelial Papilloma	3·36	6·5
,, Adenoma	5·04	9·3
,, Total	8·40	15·8
Total Innocent	42·10	43·5
MALIGNANT TUMOURS		
(1) Sarcomata	18·4	9·1
(2) Epithelial (*a*) Squamous	20·16	20·8
,, (*b*) *Carcinomata*	19·32	26·6
Total	39·48	47·4
Total Malignant	57·9	56·5

simple epithelial ones become carcinomatous. The two series lend no support to the view that malignant tumours are rare in the indigenous races of India, although the great majority of them live in a primitive manner.

The various forms of tumour showed great differences in their incidence in the two countries, only the more striking of which can be mentioned here. The excess of simple connective tissue tumours in India was essentially due to the large number of fibrous and unstriped-muscle tumours, and the excess of the sarcomata to the small round-celled variety. The excess in the London series of simple epithelial tumours lay mainly with the papillomata of mucous membranes and adenomata of the thyroid and prostate. Of greater interest are the

The addition of a little orange juice to the diet of boiled milk is of great importance.

For constipation a glycerine suppository or enema every other day is the best treatment Note that when malaria is suspected it is not desirable to persist with anti malarial drugs for more than three or four days if no effect is produced on the temperature prolonged overdosage with them is by no means uncommon in cases of typhoid, and is undoubtedly harmful.

The new antibiotics, chloramphenicol (chloromycetin) and aureomycin are of value but do not prevent relapses or the chronic carrier state. They are not so strikingly effective as in the fevers of the typhus group.

Isolation of indigenous patients in their own homes is usually impracticable, though a serious effort to secure this should be made. It must be admitted, however that there is seldom much risk of spread of the infection in the household, probably because of the extent to which immunity exists among the inhabitants of most of the tropical countries. In all cases of prolonged fever occurring in children, typhoid should be suspected unless some other explanation of the disease is found. The Widal test is more reliable in children than in adults who often give anamnestic reactions.

Prevention. Europeans run great risks of contracting typhoid fever in most tropical countries, hence the universal rule of inoculating those who go to the tropics. The results of inoculation and kitchen sanitation in the British Army in India have been marvellous, the disease having been reduced to almost negligible proportions. The civil population is also much less affected than formerly, but much remains to be done before they achieve so great a reduction in incidence as has been secured in the Army. Repeated inoculation, kitchen hygiene, the look-out for carriers among servants, and the control of flies are important steps for the elimination of typhoid fever. A simple procedure which is seldom carried out is to provide a basin of Izal or Cyllin solution (1 in 200) and to insist that all servants should disinfect their hands in this before starting each spell of duty.

Infections of the Urinary Tract

Infections of the urinary tract are very common in the tropics, especially those caused by *Bacterium coli* and it is specially important that these should be detected now that various drugs such as the newer antibiotics have been found so successful in treatment.

B. coli can often be detected by microscopic examination of perfectly fresh samples of the urine with dark-background illumination which in many cases readily reveals the motile organisms. When cultures of the urine are needed great care must be taken to avoid accidental contamination even when catheter specimens are employed

Almost all the forms of urinary tract infection are responsive to

typhoid B in the tropics ; it runs a longer and milder course as a rule, but can only be distinguished from paratyphoid B and typhoid by cultural tests. A large proportion of the cases of prolonged pyrexia in children is found to be due to fevers of the typhoid group ; Widal tests carried out in unselected groups of people show a considerable percentage of positives, and it is well known that Europeans who go to the tropics run great risk of infection. Probably infection with bacilli of the typhosus group is so common that most of the people of tropical countries suffer from the disease in early childhood, and so the adult population are immune to a great extent, but a number of them continue to be carriers of infection throughout their lives.

Typhoid fever among adults is far from uncommon, but we rarely or never see epidemics such as would be expected to occur among susceptible populations living in insanitary conditions.

An important feature of the disease is that variations from the classical types are common, the onset is often sudden, the fever irregular in its course, and constipation is the rule rather than the exception. In paratyphoid the duration of the fever may be as short as eight to ten days.

For the diagnosis of the disease early blood cultures are needed. Every practitioner in the tropics ought to make a rule of obtaining early blood cultures in all cases of doubtful fever, whenever this is possible.

The Widal test is of less value, especially if single tests are relied on, as a considerable proportion of the unselected population will give positive responses. Even a rise in the titre during the course of the fever is not absolutely diagnostic, as any agglutinins which happen to be present before the onset are likely to increase in amount during the course of any form of pyrexia, especially in fevers of the typhus group.

The most important point in treatment is to place the patient under proper care, in hospital if possible. The great difficulty in treating indigenous typhoid patients in their own homes is to secure proper nursing and diet. The patient often objects to take proper nourishment and his relatives frequently give quite unsuitable articles of food ; many patients die of actual starvation because their attendants do not insist on their taking a diet containing sufficient amounts of calories, proteins and vitamins. An essential point is to keep accurate records of the amount of milk taken during the course of each day, especially in the case of children. A common mistake in treatment is the employment of antipyretic drugs to lower the temperature—the relatives of patients usually estimate the value of treatment by the rapidity with which it reduces the temperature so that tact and firmness are needed to persuade them to allow the fever to run its course and to rely on simple methods of hydrotherapy for the control of unduly high temperature.

Eosinophilia in the Tropics

Eosinophilia occurs so frequently in association with helminthic infections that it is a very common condition in tropical countries; it sometimes occurs in persons who are free from any discoverable disease and by itself it cannot rightly be called a disease.

In recent years a syndrome now called **Tropical Eosinophilia** was first described by Frimodt Moller in South India as a "pseudo-tuberculous disease of unknown ætiology" in which chronic low fever, bronchitis, asthmatic attacks and the presence of numerous small infiltrations of the lungs seen by X ray examination are the chief features, apart from the occurrence of a pronounced degree of leucocytosis in which 20-80 per cent of the leucocytes are eosinophiles. A condition called Löffler's syndrome had already been described in Switzerland; this was attributed to the passage through the lungs of the larvæ of *ascaris lumbricoides* and it differed from tropical eosinophilia in being of shorter duration The importance of the tropical eosinophilic syndrome is that it is often mistaken for tuberculosis of the lung and that it can usually be cured by a short course of injections of neoarsphenamin given in weekly doses starting with 0·15 gm. and increasing by 0·15 gm. each week till the dose becomes 0·45 gm. In Ceylon the cause has been suspected to be the presence of minute mites in the bronchi, but apart from a strong suspicion that the condition is one of allergy to some substance of microbic or other origin the ætiology remains doubtful. Cases have been reported from North and Central Africa, China, the Philippines and the South U.S.A. Coastal and other places with a hot and moist climate are chiefly affected.

J. W. D. MEGAW

treatment by aureomycin, and presumably also by chloramphenicol (chloromycetin) so that in cases of doubt treatment by one of these drugs may be diagnostic as well as curative ; their present high cost is, however, a serious drawback.

Smallpox

Severe smallpox is still very common in most tropical countries in spite of all the efforts that are made by public health authorities. Whatever justification there may be for avoiding routine vaccination in some western countries it is exceedingly foolish to visit most tropical countries without being recently vaccinated.

The disease called Alastrim is a mild form of smallpox which occurs in some tropical countries and has a fatality rate of 1 per cent. or less, but in most places the fatality rate of smallpox among unprotected persons is 10–20 per cent.

Venereal Diseases

In most tropical countries syphilis is extremely common ; the course of the disease is very similar to that seen in temperate climates ; there is little evidence of the existence of any special strains of the parasite, distinct from those of Western countries.

A common late manifestation in India is syphilitic paraplegia ; syphilitic aortitis is by no means rare. Curiously enough, cases of tabes dorsalis and dementia paralytica are rare in the tropics.

There is some evidence that an attack of yaws is protective against syphilis. This is probably due to the close relationship which exists between the causal organisms, which some experts still regard as being the same.

Some countries in the tropics are remarkably free from venereal diseases, for example, the Punjab and some other rural areas in India ; the seaports are severely affected, so also are towns which attract large numbers of Hindu pilgrims.

Scarlet Fever

This is rare everywhere in the tropics. The disease has often been introduced into India, but hitherto it has failed to secure a foothold. Some of the towns of China, like Shanghai and Peiping, have in recent times been severely affected with scarlet fever, which runs a more virulent course than it does in Western countries where for some reason it has become much milder than it used to be.

Dental Diseases

Dental caries is less common than in temperate climates, but on the other hand pyorrhœa alveolaris is exceedingly common in the tropics where it seems to be responsible for a great deal of ill-health.

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CHAPTER XXVII

HINTS ON THE USE OF THE MICROSCOPE

THE microscope plays so essential a part in modern medicine that it is surprising to find that very few medical men have been instructed in the proper manipulation of the instrument. Most of them learn its use by rule of thumb, and so fail to get the best results.

These notes are not intended to be a complete guide to the use of the microscope, but merely to call attention to some points which are often neglected.

Most of the modern microscopes are so good that it is quite safe to buy an instrument from any reputable maker.

For everyday use a small model is quite sufficient. It should have coarse and fine adjustments, a triple nosepiece, a focussing substage condenser, three eyepieces, and three objectives, of about $\frac{2}{3}$-inch, $\frac{1}{4}$-inch or $\frac{1}{6}$-inch focus, and an oil-immersion lens of $\frac{1}{10}$- or $\frac{1}{12}$-inch focus.

If dark-field work is to be done a special condenser is needed.

Most workers prefer to have a mechanical stage, but this is not essential.

If a more complete equipment is desired, a quadruple nosepiece may be substituted, and an extra low-power objective of $1\frac{1}{2}$-inch focus should be added: a low-power oil-immersion lens of $\frac{1}{8}$-inch focus is a useful addition for dark background work; this should have a numerical aperture of 0·85 to 1·0.

For special work a drawing apparatus of the Abbe type, and two micrometers, one for the stage, the other for the eyepiece, are needed.

If it is necessary to economise to the utmost degree, a good cheap model can be had from most makers; in this case the focussing movement to the substage condenser, the mechanical stage and the dark-background condenser will have to be dispensed with, and the immersion lens will be of a cheaper type with low numerical aperture.

In using the microscope the student's first step to knowledge is a realisation that he is dealing with a scientific instrument which will not give proper results unless it is handled with skill. Approach the microscope with caution and respect, first see that all the lenses are clean, hold them up to the light and examine them from the front with a pocket lens or with the $\frac{2}{3}$-inch objective. If the front surface of a lens is dirty, wipe it with a clean soft cotton or linen handkerchief or with special lens paper. Saliva is the safest solvent for cedar-wood oil which has been allowed to dry on the surface of a lens, but a clean cloth lightly soaked with xylol may also be used very cautiously. Alcohol should not be employed for cleaning a lens or any other part of the microscope. If the back surface of a lens has become dusty,

indistinct picture with dark shadows instead of a clear transparent colour image.

To check the proper opening of the diaphragm *remove the eyepiece* and look down the tube of the microscope; you will see a brightly lighted circle in the back of the objective. When the diaphragm is closed down this is reduced to a pin point of light; when the diaphragm is fully open the circle fills the whole of the back of the lens.

The most suitable diaphragm opening for most purposes is obtained by adjusting the diaphragm so that the maximum circle of light is reduced in diameter by about one-quarter. When the diaphragm opening is reduced to a pin point, only the central part of the lens system plays a part in forming the image, and therefore the greater part of the effective aperture of the lens is wasted; if the diaphragm is wide open, extraneous light enters the lens and causes fogging of the image. When the correct diaphragm opening for the low-power lens has been found, it is advisable to put a mark on the condenser rim to show the proper position of the lever which actuates the diaphragm. This is only suitable for the lens in question; it will be quite wrong for the high-power lens.

Next focus the object with the high-power lens; *if this is done without* changing the diaphragm opening it will be found that the image is badly lighted and shadowy. The diaphragm is now opened till the image becomes clear; the correct opening can be checked in the same way as for the low power. The position of the lever for the high-power lens can also be marked.

These instructions must always be followed when dry lenses are used for examining stained specimens. When the condenser has once been focussed the only adjustments needed when the power is changed are to focus the specimen and adjust the lever of the diaphragm to the position suitable for the objective which is being used. Slides of nearly the same thickness should always be used, otherwise a fresh adjustment will have to be made of the focus of the condenser every time the slide is changed.

If the microscope has a draw-tube, this must be set to the tube-length prescribed by the makers. Many microscopes are now supplied without draw-tubes; in this case no adjustment is possible or necessary.

Note that the above adjustments must be made in the proper order: (1) focus the specimen; (2) focus the condenser; (3) adjust the diaphragm opening.

If an attempt is made to find the correct adjustment in the wrong order of sequence, failure will result.

To learn how to use the oil-immersion lens take a stained blood film, preferably uncovered, though it may be mounted in Canada balsam and covered with a very thin coverslip. First find a suitable part of the field with the lower-power lens, then put a drop of cedar-wood oil on the film, open the diaphragm of the condenser to the

fullest extent, swing the immersion lens into position and lower it till it dips into the drop of oil, raise the microscope tube very slightly with the coarse adjustment, but avoid breaking contact with the oil, then apply the eye to the eyepiece and *very cautiously* focus downwards with the coarse adjustment till the object comes into view; complete the focussing with the fine adjustment. Make certain that part of the film is in the centre of the field: this is ensured by first locating the object with the low-power dry lens and seeing that a suitable part of the film fills the field of view. Note that the oil immersion lens needs the fullest beam which can be transmitted by the condenser. Great care must be taken to avoid bringing the delicate front of the immersion lens into forcible contact with the slide, as there is a serious risk of dislocating the front lens and thus necessitating a costly repair. To avoid this damage some workers advise racking down the tube till the lens is almost in contact with the film and then focussing upwards till the object comes into view. If the object is not clearly seen, it is likely that an air-bubble has been formed between the front lens and the object; if this has happened, drain off the oil from the slide and wipe the front of the objective, then put a fresh drop of oil on the slide.

Always begin with the low power eyepiece, this gives a large and bright field of view; higher power eyepieces can be used afterwards to make out the details of any object, but as a general rule the low-power eyepieces are best for all round work.

Before the microscope is put away, be careful to wipe off the cedar-wood oil from the front of the lens with a clean soft cotton handkerchief; do not scrub the lens vigorously lest you damage the fine polish of the front surface. Special lens paper just moistened with xylol may be used for cleaning off the immersion oil; first wipe off the surplus with a dry piece of paper, then apply a piece which is moistened with xylol, and finally rub gently with another dry piece of the paper. The crude method of using a little saliva and a clean handkerchief is quite effective. If cedar-wood oil should get on the condenser or mechanical stage, clean it off at once with a soft clean cloth, using a little xylol if the oil has become thick. The immersion oil must be carefully protected from dust, evaporation, and moisture. Keep the bulk of the oil in the original bottle and pour out only a little at a time into the container. See that the cap of the container fits well so that dust is excluded and evaporation prevented. When the oil gets thick, wash out the container with xylol, and put some fresh oil into it. The lens will not give the best results unless the oil is of the right consistency. Oil that is too thick has not the proper refractive index.

When examining *unstained preparations* such as bacteria in a hanging drop, moist blood preparations, etc., there is little advantage in using the oil immersion lens; the dry lenses are much more convenient and less messy. Find the specimen first with the low-power

dry lens, stopping down the diaphragm aperture to a very small size, then turn on the high-power dry lens and arrange the diaphragm of the condenser so that the unstained objects appear as distinct shadows; the suitable condenser opening will be much smaller than when stained objects are being examined.

The concave mirror may be used for unstained specimens; the condenser being racked down out of focus, but it is more convenient to get the suitable illumination merely by stopping down the diaphragm as in this case the only adjustment needed for changing over to a stained specimen is to open the diaphragm to the appropriate degree.

Daylight is the best illuminant for most tropical countries, but if artificial light is necessary, an opal-glass bulb such as Philips' "argenta" is a convenient source of electric illumination. A flat-wick oil lamp can also be used; for detecting the sharpest details with high powers the lamp should be turned so that the edge of the wick points towards the microscope. This method of illumination has the drawback of lighting up only a small part of the field when low powers are used. Never use direct sunlight nor too strong a light; these damage the sensitiveness of the retina. The source of light should never have a pattern; even a frosted bulb does not give so suitable illumination as a bulb of opal glass. When using daylight, arrange the microscope so that when the condenser is in focus and a low-power objective is in use the whole field of the microscope will be evenly illuminated. If the microscope is at a distance from a window with small panes, the pattern of the window will form the background, and so will interfere with the image. In designing laboratories this point is often overlooked, to the detriment of the work which is done; the size of the window panes should be such that every microscope in use can have a fully illuminated field, even when the $\frac{2}{3}$-inch objective is used. Some laboratories in the tropics have too many windows; in this case the great expanse of glass makes the room hot and causes glare. In a small bacteriological laboratory in which only the front bench is used for microscopical work the only light that is needed comes from the lower part of the window. If the upper part is screened with a blind, or painted lightly with blue paint, heat and glare will be greatly reduced.

Magnification and Numerical Aperture. Most people think of the "power" of a lens in terms of magnification, but the capacity of an objective for revealing details of structure depends entirely on its numerical aperture or "N.A.," provided, of course, that it is well made in other respects.

The N.A. of an objective is a measure of its capacity for making use of the cone of light which is available for illuminating the object and forming the image. In technical terms it is defined as "the sine of half the angle formed by the maximum cone of light which can be used by the objective in forming the image." For example, if the

objective can deal with a cone of light forming an angle of 80° its N.A. is the sine of an angle of 40°, viz., 0·64.

Very high magnifications can easily be secured merely by employing high-powered objectives and eyepieces but the highest USEFUL magnification depends solely on the size of the N.A., provided that the lens is first-class in other respects.

Any increase in the magnification beyond the limits fixed by the size of the aperture is obtained at the cost of clearness of definition and so is of no value in the detection of details of structure.

For the objectives in ordinary use the limits of useful magnification are as follows: for the low-power with about 0·20 N.A., 150; for the high-power dry lens with 0·65 N.A., 400 to 500; for the oil-immersion lens with N.A 1·20 to 1·30, 800 to 1,000. Attempts to see more detail by using higher magnifications than these are usually futile; the object appears larger, but owing to diffraction and other disturbing effects the image is no longer a true representation of the object. Similar falsification of the image is caused by lengthening the draw-tube to obtain higher magnification, especially in the case of high-power objectives. All lenses are corrected for use with a stated length of draw-tube which must be used to get clear images.

The importance of the N.A. of objectives is shown by the following example, the ordinary ⅙-inch objective has an N.A. of about 0·65 and has a useful magnification of 500, but a special ⅓-inch objective can be obtained which has the same N.A. and will give as good an image at the same magnification by using an eyepiece of double the power. The latter objective has the advantage of being suitable for searching the object at low magnification and then, simply by changing the eyepiece, it will reveal every detail that can be seen with the one-sixth lens. It also has a longer working distance and can be used with a blood-counting cell: unfortunately it is very costly.

When cost is not a serious consideration better results can always be obtained by using dry objectives of low initial magnification and high numerical aperture.

The oil-immersion lens is the most important item in the equipment; this has a very large N.A. of 1·0 to 1·4 and so is capable of revealing far more than any dry lens.

Full advantage cannot be taken of apertures higher than N.A. 1·0 with the usual type of Abbe condenser because this cannot provide a cone of light with a higher aperture than 1·0 unless it is used on the immersion principle by placing a drop of oil between the front of the condenser and the back of the slide; this is so troublesome that it is seldom done except for specially exacting research work. Those who cannot afford the more expensive oil-immersion lenses need not hesitate to use the cheaper and more robust kinds with apertures of about 1·0.

As is the case with dry lenses the capacity of immersion objectives

depends solely on the N.A.; one of the most powerful lenses in the world is a ⅛-inch apochromatic with a N.A. of 1·4; its lower initial magnification is a great advantage and it can be used with very high-powered eyepieces to give the same useful magnification as is obtainable with the one-twelfth inch lens.

Apochromatic oil-immersion lenses are not recommended for use in the tropics; some of the glasses used in their construction become cloudy after two or three years' use.

Fluorite lenses which are not appreciably inferior in performance do not suffer from this serious defect and are decidedly better than ordinary achromatics.

They cost about twice as much and are only needed for photography and specially delicate research work.

Some workers prefer the modern binocular type of instrument which is less tiring to the eyes; it does not give any increase in definition of the image and has two drawbacks in addition to the extra cost; one is that it involves some loss of brightness of the image and the other that the prisms are liable to become clouded with dust and fungus growths.

Those who prefer to use a binocular ought to get one with interchangeable monocular and binocular tubes; by doing so they can have the advantages of both kinds of instrument.

For entomological work the Greenough type of binocular has great advantages. It is a true binocular, being made of two microscopes working side by side; solid objects stand out in full relief, the image is erect and the working distance is great. For dissection work it is far better than the ordinary microscope, even when this is fitted with a binocular tube. It can only be used for low-power work as the system of construction does not admit the use of objectives with large apertures.

The largest useful magnification is about 100 diameters; anything more than this is "empty" magnification.

With two pairs of objectives of about 60 and 30 mm. focus and three pairs of eyepieces a range of magnification from 10 to 100 is obtained.

Dark-field Illumination. This is of special value in the early diagnosis of syphilis, but it has a wide application in the search for spirochætes and other bodies which are difficult to see, even in well-stained specimens. A special condenser is used in which all the central cone of light is cut out, the only rays admitted being those which pass so obliquely that they do not directly enter the objectives at all.

The dark-field condenser should be got from the maker of the microscope which is in use. It must be accurately centred.

Illumination should be from a small but very intense source of light. The bulb of a 6-volt motor car head-light is suitable; this is supplied with current from a 6-volt accumulator or from a transformer connected with an alternating-current domestic supply. Heavily

insulated wires should be used to connect the lamp with the transformer.

The lamp is housed in a ventilated box with a small window which allows the light to fall only on the mirror of the microscope. The room should be as dark as possible; extraneous light lessens the sensitiveness of the retina.

The lamp is placed close to the microscope and is fixed firmly in its box: the slightest movement upsets the illumination. The slide must be scrupulously clean, and must be of the correct thickness, generally about 1 mm. or less. The coverslip must also be very clean and of good quality. The moist preparation must be thin and almost transparent; leucocytes and red blood corpuscles cause a great deal of dazzle by reflecting light into the objective, while air-bubbles are fatal to good results. Contact is made between the front of the condenser and the back of the slide with cedar-wood oil (water can be used with some types of dark-field condensers). The condenser is centred and focussed with a low-power dry lens, then the high-power dry lens is used.

A good dry lens gives excellent results, but somewhat better definition is obtained by using a special low-aperture oil immersion lens of about 0·9 N.A. and $\frac{1}{8}$-inch to $\frac{1}{10}$-inch focus.

The $\frac{1}{12}$-inch lens of 1·3 N.A. can be used, but a special diaphragm must be inserted to cut down the aperture. This fitting is supplied at a small extra cost by all makers: it should be removed when the lens is used for ordinary purposes.

Workers in a laboratory will find it very convenient to keep a separate microscope fitted with dark-field illumination, by doing so much time is saved because the proper adjustment of the condenser and lighting is a lengthy procedure

For dark-field illumination with low-power objectives special centre stops can be had for the ordinary substage condenser; these are useful in the examination of flagellates in the living condition.

Other Hints. Keep both eyes open when using the microscope and so avoid eye strain. A screen of blackened cardboard can be fixed on the microscope tube to shade the eye which is not in use, or a special eye-shade can be bought from microscope dealers. It is a good practice to use both eyes in turn, but most workers can see details more clearly with one of their eyes, and so refuse to accept this advice.

An almost universal mistake is to use too high magnifications: the low-power eyepiece should always be used for searching the specimen, it gives a brighter image and includes a larger area of the specimen in the field of view than the higher power which should be used chiefly for the detection of minute details.

One of the eyepieces should have a magnifying power of 5 to 6, the other of 10. A third eyepiece magnifying 15 times can be used if the high-power dry lens is of $\frac{1}{4}$- or $\frac{1}{6}$-inch focal length with a high N.A.;

when a $\frac{1}{6}$- or $\frac{1}{7}$-inch lens is used the eyepiece should never be stronger than 10 or 12 initial magnification. When not in actual use the microscope should be kept in its case or covered with a bell-jar or other protection.

Coverslips of about 0·17 mm. thickness should be used with dry lenses, which are corrected for slips of this thickness. If a specimen has a thicker cover the tube-length should be shortened to obtain the best results with the high-power dry lens.

Some workers demand that the objectives should give a "flat field," viz., that the definition should be equally good all over the field of vision. This can be obtained with objectives of low N.A. and low magnification ; the higher the N.A. the less flat is the field, so that the value of a lens can only be judged by the clearness of definition at and near the centre of the field.

Depth of focus is another property that cannot be obtained with powerful objectives, it varies inversely with the N.A. and is only of special value for dissection work.

The Greenough binocular with its low aperture gives a greater depth of focus than standard microscopes working at the same magnification. For special technical methods such as fluorescent staining or phase-contrast illumination a modern book on Microscopy should be consulted. Practical instruction by an expert is essential if the best results are to be obtained.

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CHAPTER XXVIII

GENERAL REMARKS. DIAGNOSIS OF FEVERS. CASE-TAKING

GENERAL REMARKS ON MEDICAL PRACTICE IN THE TROPICS

DESPITE the drawbacks connected with medical practice in the tropics there are advantages which many workers have found to be adequate compensation for the sacrifice of the comforts of civilised life in a favourable climate. Special attractions are the far greater opportunities for the prevention and cure of disease and for research into the many unsolved problems that still exist.

A sound training in the methods of investigation that can be carried out in an improvised laboratory is an essential preliminary to work in the tropics where expert help is seldom available at short notice. Many important additions to knowledge have been made by medical men who have made a practice of carrying out such investigations for themselves, and it often happens that an *immediate diagnosis* means life instead of death to the patient.

THE DIAGNOSIS OF FEVERS IN GENERAL IN THE TROPICS

The fevers in the tropics may be divided into three groups :—

(1) Those which can be diagnosed with certainty by the use of recognised methods of investigation.

(2) Those which can be diagnosed with a high degree of probability.

(3) Those which remain doubtful or unknown even after exhaustive examination.

Cases falling into the third group constitute a small minority, and fortunately most of them end in recovery when Nature is allowed to work out a cure.

The chief points in the diagnosis of fevers are :—

(*a*) The history of the patient, including a knowledge of the places in which he has been living, of possible exposure to infection from other persons or from animals and of the prevalence of fevers in the localities where he has been living or travelling.

(*b*) A complete physical examination to determine whether there are any indications of a helpful nature in the skin, throat, respiratory passages, lungs, liver, spleen or other organs of the body.

(*c*) Examination of the blood, urine, fæces and sputum.

Examination of the blood should never be omitted even when the cause of the disease has already been detected. The most important methods are :—

(1) Search for parasites in stained smears ; in suspected malaria this should be repeated at frequent intervals if the first search has been fruitless.

(2) Blood cultures ; these are of great value in the early stages of fevers which have not been diagnosed ; cases of typhoid and paratyphoid fevers which would otherwise escape detection are often discovered ; even negative findings are usually helpful.

(3) Agglutination tests, especially with the typhosus group of organisms and the three chief strains of *Proteus OX*.

Early tests should be made so that significant rises in titre may be detected if they occur at a later stage.

(4) Total and differential leucocyte counts very often give useful clues to the nature of the fever. Owing to the stress which has been laid on this method of examination by L. Rogers, tropical workers have made far more use of leucocyte counts than their colleagues in cold climates.

(5) Animal inoculation tests : these will certainly be much more widely used in future years than has been the case in the past. Many cases of leptospiral fever have escaped detection owing to the failure to carry out a simple animal test.

(6) Examination of the fæces should be carried out as a routine measure. Pathogenic protozoa and the ova of intestinal parasites can often be discovered even when no other indications of their presence have been detected.

(7) Urine and sputum examination should always be carried out if a diagnosis has not been reached by other methods. For routine purposes the ordinary naked-eye urine tests are sufficient, but in doubtful cases microscopical and cultural tests are often of great value.

(8) The pulse, respiration and temperature should be recorded every two hours, if possible, but in any case every four hours.

(9) Till the patient has completely recovered, a complete overhaul should be made at frequent intervals ; fresh developments of an important kind often develop in an insidious manner. It is most humiliating to have these pointed out by a colleague or consultant.

(10) In doubtful cases think of all the possible causes of the fever and exclude them one by one.

No harm is done by going straight for the most likely cause, but every effort must be made to avoid the natural tendency to form preconceived ideas about the diagnosis and then fit in the evidence to support the favoured opinion. If a " lightning diagnosis " is made it should always be subjected to rigorous criticism before being accepted.

(11) A common error is to be satisfied with the discovery of positive evidence of one disease ; having found a pathogenic organism, do not jump to the conclusion that this is the real or the only cause of the patient's condition. In many cases the patient will be found to harbour the parasites of several diseases, and the first to be discovered is by no means certain to be the most important.

Malaria parasites are often found in patients suffering from typhoid fever, kala-azar or other diseases ; positive Widal or Wassermann reactions may mislead by distracting attention from co-existing

diseases. The only safe rule is to assume that the patient harbours several infections and never to rest content with one positive finding even when it appears to account for all the symptoms. The patient may be adequately treated for malaria or typhoid fever, but if he still has amœbic or helminthic infection he cannot be regarded as having received proper attention.

Summary of the Chief Diagnostic Features of the Common Fevers of Tropical Countries

	Chief Diagnostic Features	Other Points which are often Helpful in Diagnosis
Malaria	Finding the parasite in the blood	(1) Type of fever; (2) Place of residence; (3) Therapeutic test; (4) Enlarged spleen
Kala-azar	Finding the parasite in thick blood-smear or spleen puncture fluid	(1) Aldehyde test; (2) Place of residence; (3) *Leucopenia*; (4) Enlarged spleen; (5) Type of fever
Sleeping sickness	Finding parasite in gland puncture fluid	(1) *Gland enlargement*; (2) Place of residence
Typhoid and paratyphoid group.	Early blood culture	(1) *Widal test*; (2) *Stool* and urine culture; (3) Type of fever
Fevers caused by *B. coli*	Blood and urine cultures	Serum agglutination tests.
Undulant fever	Blood culture	Agglutination test
Tuberculosis	(1) Finding the bacillus in sputum in *some cases*; (2) *Physical signs in* some cases; (3) *X-ray examination.*	(1) Tuberculin test in infancy; (2) Exposure to infection; (3) Exclusion *of other causes.*
Cerebro-spinal fever	Finding meningococcus in lumbar-*puncture fluid*	General symptoms.
Influenzal and other *respiratory infections.*	*Physical examination or sputum examination, according to circumstances.*	(1) Exposure to infection; (2) Type of fever.
Septicæmic fevers	Blood cultures	Cardiac signs in some cases.
Syphilitic and yaws fevers	Wassermann or Kahn test	(1) Therapeutic test; (2) Physical signs in some cases.
Smallpox and other exanthematous fevers.	Rash	(1) Type of fever; (2) Exposure to infection.
Relapsing fever	Finding spirochætes in blood smears	(1) Type of fever; (2) *Presence of lice* or ticks; (3) Agglutination tests.
Weil's disease-group	(1) Blood culture; (2) Animal-inoculation.	(1) *Environmental conditions*; (2) Jaundice in some cases.
Dengue and sandfly fever-group.	General characters of fever with early leucopenia and exclusion of other causes.	(1) *Local* occurrence of other cases; (2) Rash in some cases.
Yellow fever	General characters of fever	Local occurrence of other cases
Zootic typhus fevers	(1) Agglutination tests against the *Proteus OX* group of organisms; (2) Characters of fever and rash; (3) Finding attached tick or mite in some cases.	Local conditions, especially the known occurrence of other cases in the locality and exposure to risk of bite by infected ticks, mites or fleas.
Heat-fever	Suitable climatic conditions combined with general character of the fever and exclusion of other causes.	
Entamœbic fever (Amœbic hepatitis).	(1) *Local signs and symptoms*; (2) *In* absence of these, the response to emetine may be the only means of *diagnosis.*	(1) *Leucocytosis*; (2) Sometimes a history of dysentery; (3) Sometimes entamœbæ found in stools.
Q fever	Complement-fixation test.	Epidemiological conditions.

The table above gives a list of most of the important fevers which occur in tropical countries.

In cases of doubt it will be found useful to run through this list and consider whether the features of the disease are compatible with the possibility of its falling within any of the groups which are mentioned. Some of the fevers can at once be excluded when they are definitely known to be absent from the locality in which the patient has been living : for example, kala-azar, sleeping sickness, yellow fever, yaws, and mite typhus, have fairly definite geographical boundaries ; most of the other fevers are of widespread occurrence in tropical and sub-tropical countries. Dengue and sandfly fever can often be excluded when the climatic conditions are unsuitable for transmission by the insect vectors ; even malaria can often be excluded when the patient has not been in a place where malaria occurs.

This list is far from being comprehensive ; it must be regarded as being essentially an aid to diagnosis by suggesting possibilities which might otherwise be overlooked. The more definite diagnostic features have been placed under the heading "Chief Diagnostic Features." In most cases these are conclusive of the presence of the disease, but in a few fevers there is no absolute criterion on which a diagnosis can be based.

CASE-TAKING IN TROPICAL COUNTRIES

The clinical reports of patients treated in hospitals in the tropics are often written in so desultory a way that it is difficult or impossible to find the information needed in the study of the diseases with which they deal. The training of students and the maintenance of useful records would be greatly improved by providing case-sheets of foolscap size consisting of four pages of which the first two have printed headings on the lines of the example shown on pp. 547 and 548.

The headings would be modified to suit the conditions prevailing in different areas. The two blank pages would provide space for detailed descriptions and progress reports of the usual kinds.

The unconvential orientation of the temperature chart has the great advantage of making it possible to co-ordinate the daily changes of temperature with the summary of the other happenings of each day by keeping them on the same line.

There would be more space in the full sized chart for the abbreviated entries and the headings could be printed in the smallest type consistent with legibility.

J. W. D. MEGAW

HOSPITAL.	NUMBER in ADMISSION REGISTER.

NAME	RESIDENCE JUST BEFORE ADMISSION.	PERMANENT RESIDENCE.	NAME & ADDRESS OF NEAREST RELATIVE.

AGE	SEX	CASTE	INCOME.	NUMBER OF DEPENDENTS	ENTRIES MADE BY	DATE & HOUR OF ADMISSION.	DATE & HOUR OF DISCHARGE

DIAGNOSIS ON ADMISSION.	DAY of DISEASE.	INITIAL TREATMENT.	INITIAL DIET	DATE.	DAILY NOTES.
DIAGNOSIS ON DISCHARGE.					
RESULT.					

WEIGHT	URINE	STOOLS	PULSE	RESP.	97	98	99	100	101	102	103	104	105	106	DAY of DISEASE	CHANGE IN TREATMENT.	CHANGE IN DIET.	DATE	DAILY NOTES

AS FAR AS POSSIBLE ALL ENTRIES REFERRING TO ONE DAY SHOULD BE MADE ON THE SAME LINE. WHEN ANY MEDICINE OR DIET IS OMITTED THE NOTE SHOULD BE MADE ON THE PROPER LINE.

FIG. 85

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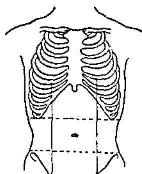
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INDEX

Notes written by *Date*
Pt. complains of
Prev. illnesses
Other cases in house or locality
Family history.
Usual diet (daily amounts of each article in ounces).
Addictions (alcohol, etc.)

PRESENT CONDITION. *Is* *nourished. Mental state is*
The face is *The patient looks*
Eyes *Tongue* *Teeth* *Gums*
Throat *Nose* *Ears* *Glands*

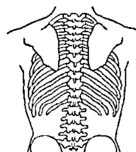
CARDIOVASCULAR SYSTEM
Pulse
Blood pressure:—
Syst.
Diast.
Cardiac symptoms



ALIMENTARY SYSTEM
Spleen
Liver
Stomach
Intestines
Rectum
Etc.

NERVOUS SYSTEM
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Sensory disturbances
Reflexes
Etc.

Cardiac physical signs



RESPIRATORY SYSTEM
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Breathing
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GENITO-URINARY SYSTEM
Symptoms
Signs

SKIN. *Rash, etc.*

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Polymorphs. per cent. *Lympho. per cent.* *Mono. per cent.*
Eosinoph. per cent. *Culture* *Serolog. tests*

SPUTUM *Amount* *Appearance* *Test findings*

STOOLS *Appearance* *Results of tests*

URINE *Appearance* *Reaction* *S.G.* *Albumen* *Sugar* *Blood*

Other special examinations and notes for which there is not enough room above:—

Abbreviations such as 0 = absent or negative; ± = slight or partial; + = present in slight degree or small amount; ++ = considerable; and +++ = great, can often be used.

FIG. 86